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(54) Heteroarylamino- and heteroaryloxypyridinamines and related compounds, a process for their preparation and their use as medicaments

Heteroarylamino- und Heteroaryloxypyridinamine und verwandte Verbindungen, Verfahren zu ihrer Herstellung und ihre Anwendung als Arzneimittel

Hétéroarylamino- et hétéroaryloxypyridinamines et composés apparentés, procédé pour leur préparation et leur utilisation comme médicaments

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Description

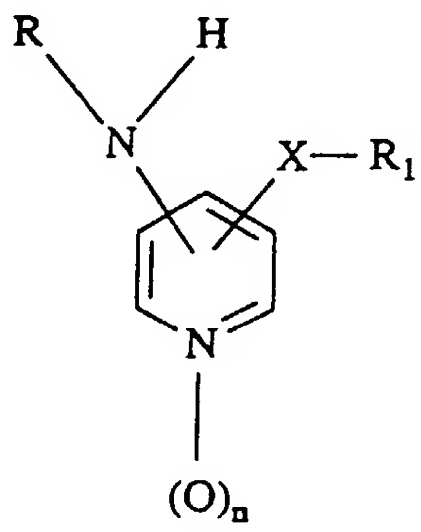
The present invention relates to heteroarylamino- and heteroaryloxypyridinamines and related compounds, a process for their preparation and their use as medicaments

DE-A- 2 015 955 discloses N-(indan-1-yl)pyridindiamine derivatives which have an antiphlogistic activity.

US-A-4 144 341 discloses 3-nitropyridinyl-indanyl-amine derivatives as intermediates in the formation of compounds having analgesic, antipyretic and/or anti-inflammatory effects.

EP-A-0 237 467 discloses the compound 4-(5-nitro-2-pyridyloxy)-indol as an intermediate in the formation of compounds having CNS activity.

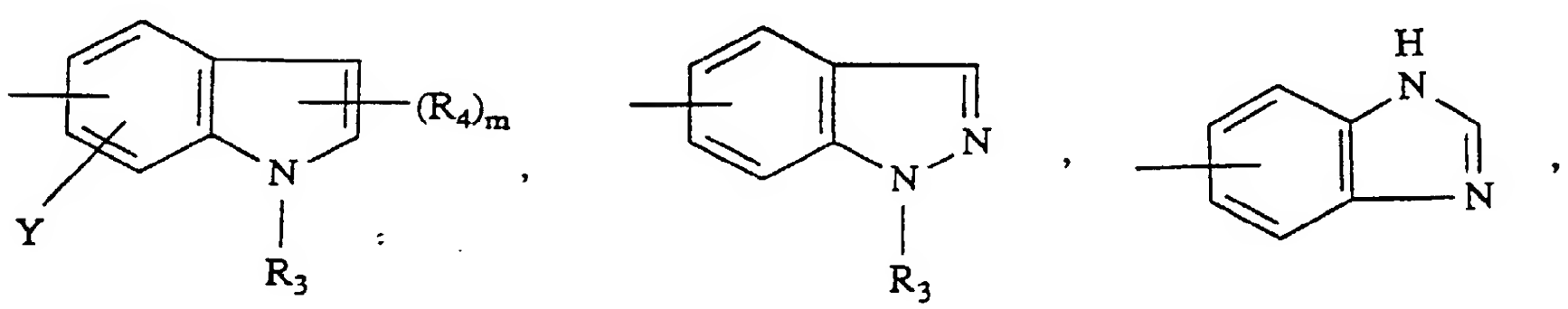
The present invention provides compounds of Formula Ia

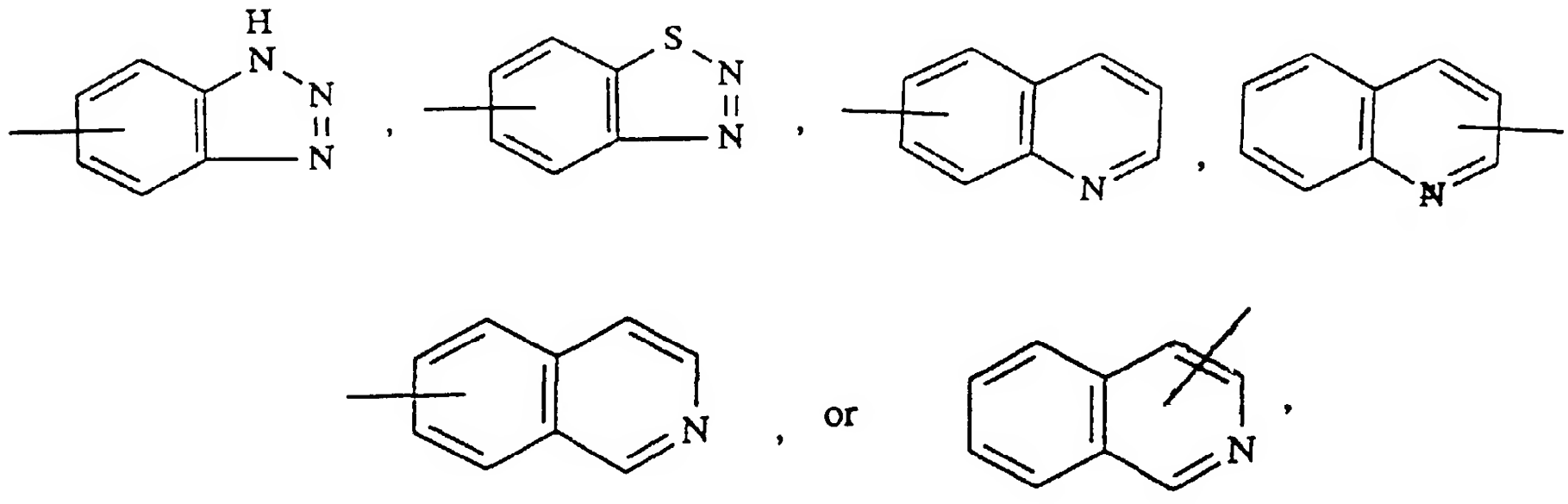


(Ia)

where

n is 0 or 1;
X is O or NR_2, R_2 being hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkylcarbonyl;
R is hydrogen, $(C_1\text{-}C_6)$alkyl, phenyl-$(C_1\text{-}C_6)$-alkyl or $(C_1\text{-}C_6)$alkylcarbonyl where phenyl is optionally mono-substituted with a $(C_1\text{-}C_6)$alkyl $(C_1\text{-}C_6)$alkoxy, halogen or trifluoromethyl group; and
R_1 is

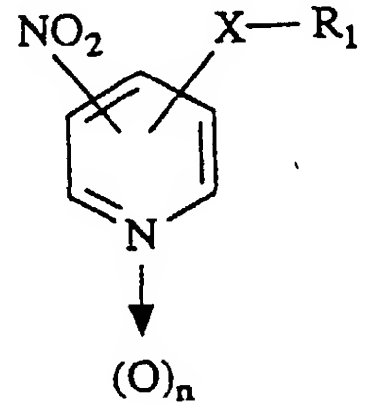




wherein R_3 is

hydrogen, (C_1-C_6)alkyl or (C_1-C_6)alkylcarbonyl; m is 1 or 2; each R_4 is independently hydrogen or (C_1-C_6)alkyl; and Y is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or trifluoromethyl;
which compounds are useful as topical antiinflammatory agents for the treatment of various dermatoses including, for example, exogenous dermatitides (e.g. sunburn, photoallergic dermatitis, urticaria, contact dermatitis, allergic dermatitis), endogenous dermatitides (e.g. atopic dermatitis, seborrheic dermatitis, nummular dermatitis), dermatitides of unknown etiology (e.g. generalized exfoliative dermatitis), and other cutaneous disorders with an inflammatory component (e.g. psoriasis).

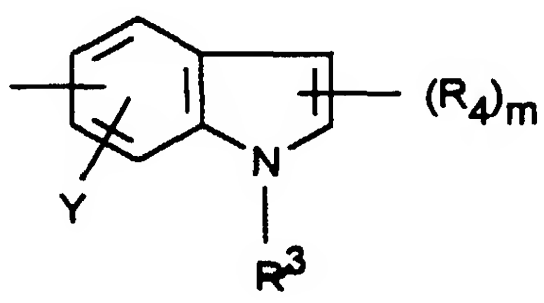
Also included within the scope of this invention are compounds of Formula Ib where n, X and R_1 are as defined above, but excluding the compound 4-(5-nitro-2-pyridyloxy)-indol, which are useful for the same dermatological applications as mentioned above and also as direct precursors of the compounds of Formula Ia.



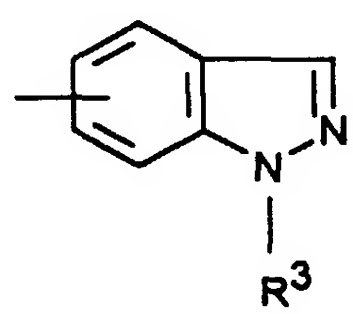
(Ib)

Compounds of Formula Ia and Ib are preferred in which

X is O or NH and R is H. Preferably also,
R_1 is



or



where Y is hydrogen or halogen, and R_3, R_4 and m are as defined above. More preferably Y is hydrogen or chlorine, R_3 is hydrogen, methyl or acetyl and R_4 is hydrogen or methyl. Advantageously the compound is of the Formula Ia where R is H and n is O or the compound of the Formula Ib where n is 1.

The present invention also provides a pharmaceutical composition which comprises as the active ingredient a compound as shown in Formula Ia or Formula Ib and a suitable carrier therefor.

The present invention also provides the use of a compound of the Formula Ia or Ib for the preparation of a medicament being effective against skin disorders.

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims.

The term (C_1-C_6)alkyl shall mean a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said (C_1-C_6)alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl. The term halogen shall mean fluorine, chlorine, bromine or iodine.

The term phenyl shall mean a phenyl group optionally mono-substituted with a (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen or trifluoromethyl group.

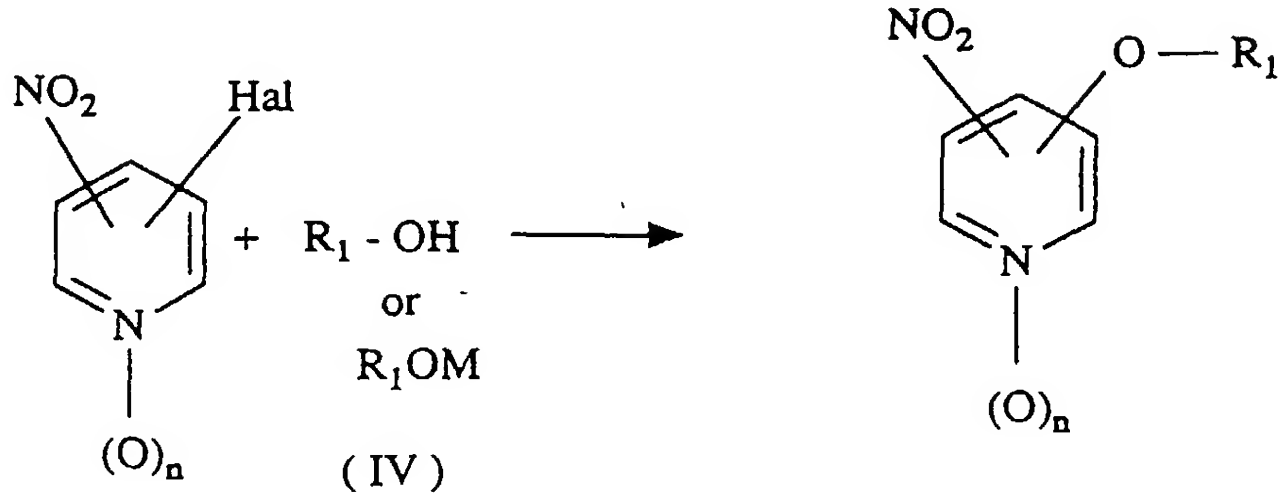
Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo, optical, geometrical and tautomeric isomers where such isomers exist.

The compounds of this invention are prepared by utilizing one or more of the synthetic steps described below.

Throughout the description of the synthetic steps, the notations R, R_1, R_2, R_3, R_4, X, Y, m and n shall have the respective meanings given above unless otherwise stated or indicated, and other notations shall have the respective meanings defined in their first appearances unless otherwise stated or indicated.

STEP A:

A compound of Formula III where Hal is F or Cl, preferably F, is allowed to react with a compound of Formula IV where M is Na, K or Li to afford a compound of Formula V.



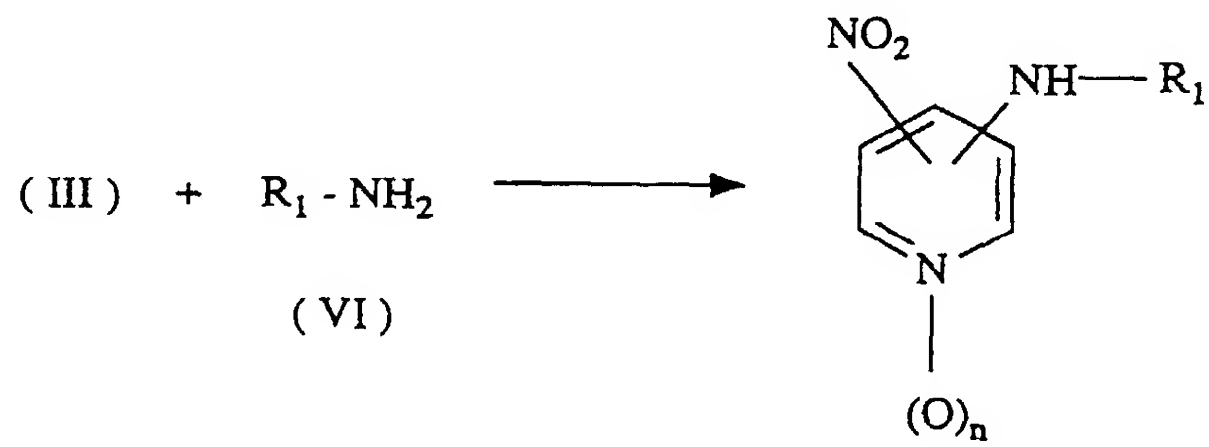
(III) (IV) (V)

This reaction is typically conducted in a suitable solvent such as ethanol, dimethylformamide, dimethylsulfoxide or N-methylpyrrolidone at a temperature of about 0 to 150°C.

3-Fluoro-4-nitropyridine-N-oxide, which belongs to the group of compounds of Formula III, is disclosed in Talik and Talik, Roczniki Chemii, Volume 38, 777 (1964). 4-Chloro-3-nitropyridine, which also belongs to the group of compounds of Formula III, is disclosed in Talik, et al., Roczniki Chemii, Volume 43(5), 923 (1969).

STEP B:

Compound III is allowed to react with a compound of Formula VI to afford a compound of Formula VII.

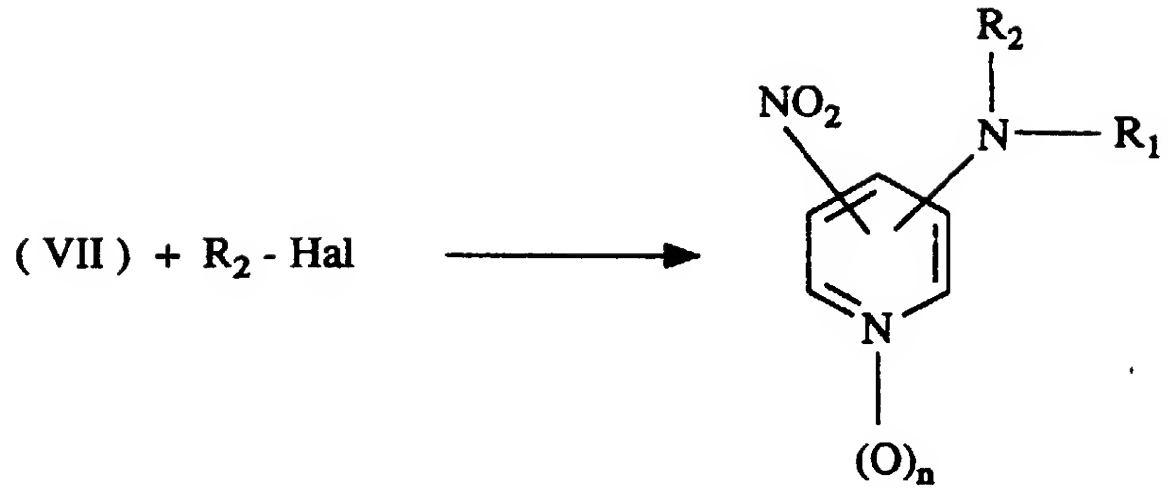


(VII)

This reaction is typically conducted in the presence of a suitable solvent such as ethanol, dimethylformamide, dimethylsulfoxide or N-methylpyrrolidone at a temperature of about 0 to 150°C.

STEP C:

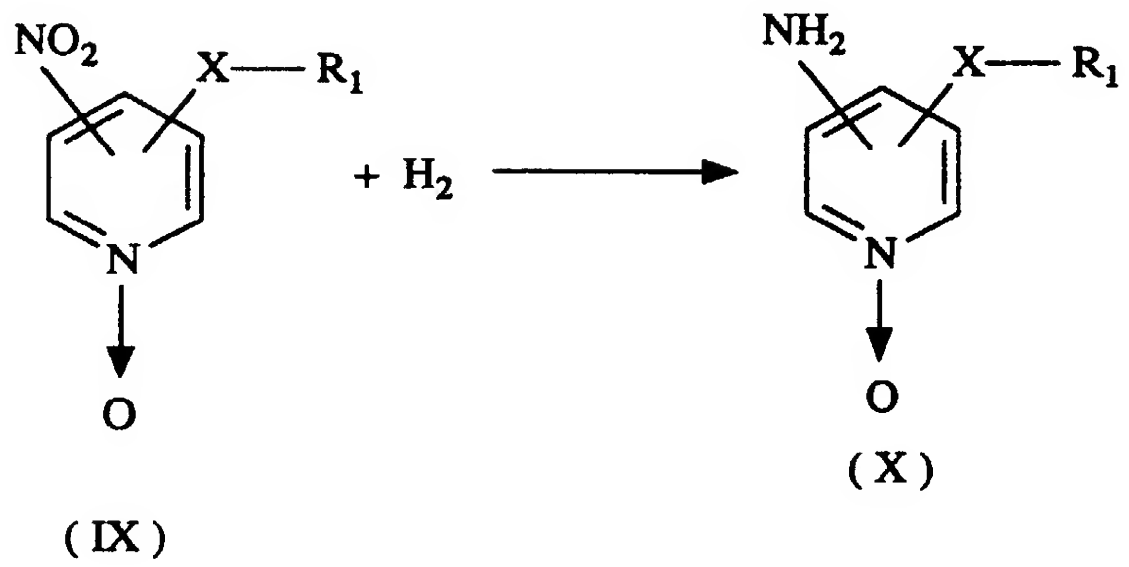
Compound VII is allowed to react with a compound of the formula, R_2-Hal, where R_2 is (C_1-C_6)alkyl or (C_1-C_6) alkylcarbonyl and Hal is bromine or chlorine in a routine manner known to the art to afford a compound of Formula VIII.



(VII) + R_2 - Hal → (VIII)

STEP D:

A compound of Formula IX which is obtained from STEP A, B or C is selectively hydrogenated to afford a compound of Formula X.

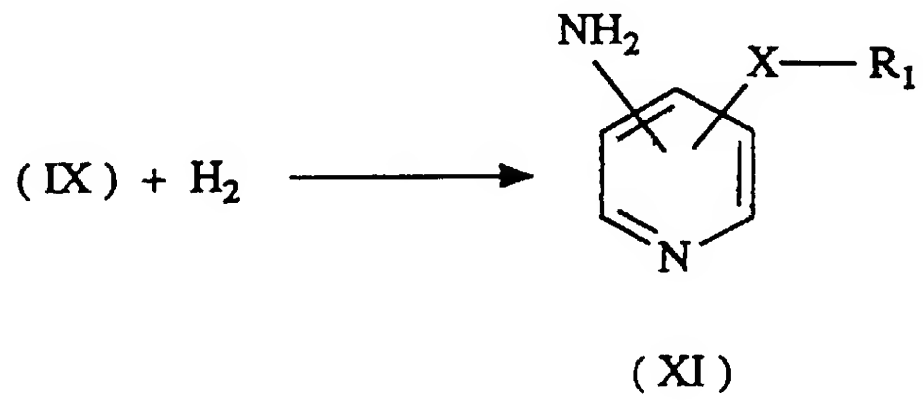


(IX) + H_2 → (X)

This selective hydrogenation is typically conducted with the aid of a suitable catalyst such as Pd/C, Pt/C or PtO_2 and a suitable medium such as ethanol at a temperature of about 20 to 80°C.

STEP E:

Compound IX is catalytically hydrogenated in a manner similar to the one described in STEP D above, except that a longer reaction period or higher reaction temperature is preferably employed, to afford a compound of Formula XI.

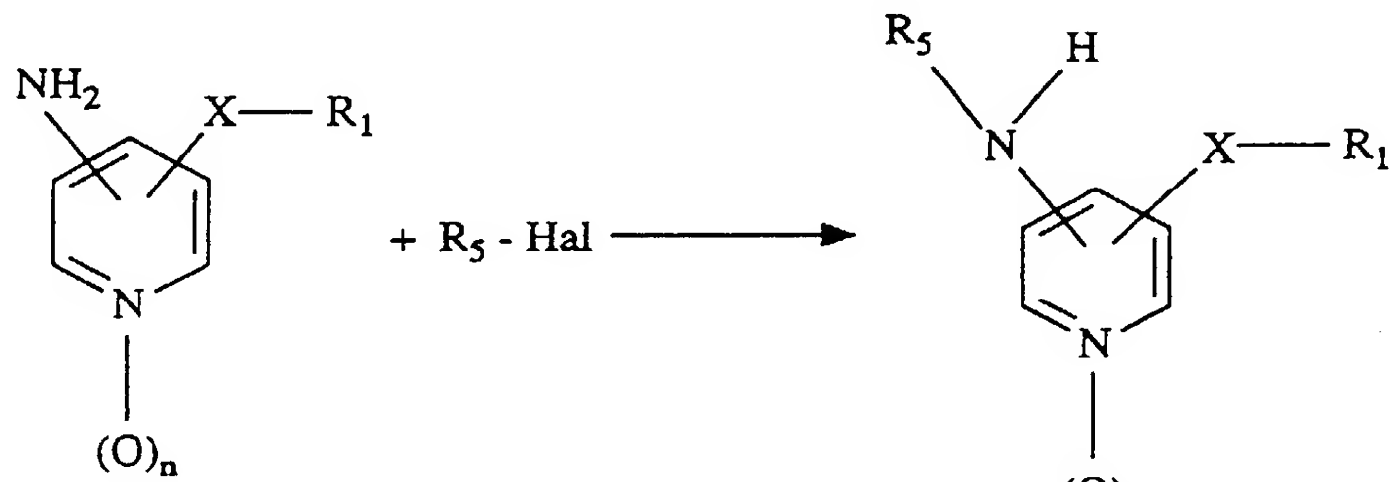


(IX) + H_2 → (XI)

Instead of using compound IX in the above reaction, one can also use compound X and conduct the hydrogenation in substantially the same manner as described above to obtain compound XI.

STEP F:

A compound of Formula XII obtained from STEP D, E or G is allowed to react with a compound of the formula, R_5-Hal, where R_5 is (C_1-C_6)alkyl, phenyl(C_1-C_6)alkyl or (C_1-C_6)alkylcarbonyl and Hal is bromine or chlorine, in a routine manner known to the art to afford a compound of Formula XIII.

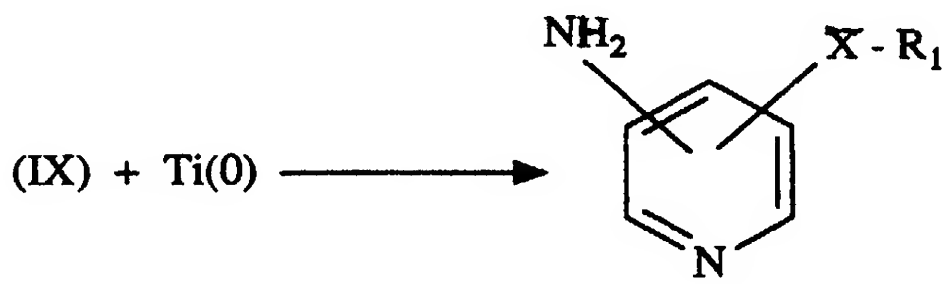


(XII)

(XIII)

STEP G:

Compound IX is reduced with a titanium (0) reagent in a routine manner known to the art to afford Compound XI.



(XI)

Typically, the titanium (0) reagent is prepared by combining a reducing agent, such as lithium aluminum hydride or magnesium metal, to titanium tetrachloride in an ethereal solvent such as tetradydrofuran, diethyl ether, diisopropyl ether, or 1,2-dimethoxyethane.

Compounds of Formula I and Formula II according to this invention are useful as topical agents for the treatment of various skin disorders such as those mentioned earlier. The dermatological activities of the compounds of this invention were ascertained with reference to the following methods.

DERMATOLOGICAL TEST METHODS

Phospholipase A_2-induced Paw Edema (PIPE)

The ability of compounds to prevent naja naja (snake venom) phospholipase A_2-induced paw edema in male Wistar rats (100-125 g) was measured. PLA_2 (3 units/paw) alone or with 0.1 M of the test compound was injected in the subplantar region of the rat left hindpaw. Immediately subsequent to the injection and at two hours post administration the paw was immersed in a mercury bath, and paw displacement was measured on a recorder via a transducer. (Standard: hydrocortisone ED_{50}=0.46 M). See Giessler, A.J. et al., ***Agents and Actions***, Vol. 10, Trends in Inflammation Research (1981), p. 195.

In Vitro Phospholipase A_2 Assay (PLA_2)

The ability of a compound to modulate PLA_2 activity (cleavage of ^{14}C-dipalmitoyl phosphotidylcholine at the 2-position to ^{14}C-palmitic acid) was quantitated in this assay. The reaction mixture contained Tris buffer (25mM), pH 8.0, calcium chloride (2.0 mM), bovine serum albumin (0.5 mg), dipalmitoyl phosphotidylcholine ($8x10^{-5}M$), (^{14}C-palmitoyl) dipalmitoyl phosphotidylcholine ($6x10^3$ cpm), porcine pancreatic PLA_2 (3.2 units) and the test compound. The reaction was run at 37°C in a shaking incubator. The reaction was quenched and an internal standard was added in order to determine sample recovery. The samples were loaded onto C_{18} columns, eluted with ethanol, and the radioactivity was then measured. (Standard: quinacrine $IC_{50}=3.5x10^{-4}M$). See Feyen, J.H.M., et al., **Journal of Chromatography** 259 (1983), pp. 338-340.

Arachidonic Acid-Induced Ear Edema (AAEE)

The purpose of this assay was to deterimine the ability of a topically-applied compound to prevent mouse ear edema induced by topical application of arachidonic acid. Female Swiss Webster mice topically received vehicle or test compound (1.0 mg/ear) on both ears (10 µl on outer and inner ears). After 30 minutes, the right ear of all groups received arachidonic acid (4 mg/ear) and the left ear received vehicle alone. After an additional 1 hour, the mice were sacrificed and an ear punch (4 mm) was taken from each ear. The difference in right and left ear punch weights for each animal was determined to assess activity. (Standard: indomethacin ED_{50} = 1.5 mg/ear). See Young, J.M. et al., ***J. Invest. Dermatol.***, 80, (1983), pp 48-52.

TPA-Induced Ear Edema (TPAEE)

The purpose of this assay was to determine the ability of a topically-applied compound to prevent ear edema induced by topical application of TPA (phorbol 12-myristate acetate). Female Swiss Webster mice topically received TPA (10µg/ear) on the right ear and vehicle on the left ear. The test compound (10 µg/ear) was applied to both ears. After five hours, the animals were sacrificed and an ear punch (4 mm) was taken from each ear. The difference in right and left ear punch weights for each animal was determined to assess activity. (Standard: hydrocortisone ED_{50}=47 µg/ear). See Young, J.M. et al., ***J. Invest. Dematol.***, 80 (1983), pp. 48-52.

Cultured Human Keratinocyte DMA Synthesis (in vitro DNA)

The effect of a compound on the proliferation of cultured human epidermal keratinocytes was measured. After incubation with a test compound for 24 hours, the cultures were pulse-labelled for three hours with 5µCi of ^3H-thymidine. The cultures were extracted for DNA successively with trichloroacetic acid and ethanol, and thereafter dissolved with NaOH. The radioactive incorporation of ^3H-thymidine into DNA was determined. (Standard: indomethacin $IC_{50}=3.8x10^{-5}M$).

Epidermal DNA Synthesis (in vivo DNA)

The influence of compounds on the proliferation of skin was assessed by determining inhibition or stimulation of DNA synthesis. HRS/J hairless mice received topical application of a compound or vehicle alone on the dorsal aspect. After 24 hours, ^3H-thymidine (25 µCi) was administered by intraperitoneal injection. After an additional hour, animals were sacrificed and the dorsal skin was removed. The epidermal layer was peeled from the dermis by heat separation. Unincorporated ^3H-thymidine was removed by washing successively with trichloroacetic acid and ethanol. Samples were centrifuged at 2,000 rpm and supernatants discarded. The epidermal sheets were then extracted with warm trichloroacetic acid and the supernatants analyzed for ^3H-thymidine incorporation by scintillation counting and total DNA by a standard colorimetric assay. (Standard: indomethacin ED_{50}=1.75 mg/animal). See Lowe, NJ., et al., **Arch. Dermatol.**, 117 (1981), pp. 394-8; and Burton, K., **Biochem. J.** 62 (1956), pp. 315-22.

Dermatological activities for some of the compounds of this invention are presented in Table 1.

TABLE 1

Compound	PIPE* (0.1 M)	PLA_2* (0.01 M)	AAEE (1 mg)	TPAEE (10 μg)	in vivo DNA (25 mg)	in vitro DNA (50 μM)
N-(4-Nitro-3-pyridinyl)-1H-indol-5-amine, N^5-oxide		-71%				
1-Methyl-N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N^5-oxide	-41%	-66%		-30%		
N-(3-Nitro-4-pyridinyl)-1H-indol-5-amine		-36%				
N-(4-Nitro-3-pyridinyl)-1H-indol-7-amine, N^7-oxide				-40%		
N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amine N^5-oxide				-78%		
N-(4-Nitro-3-pyridinyl)-1H-indazol-6-amine, N^6-oxide		-83%				
N-(4-Amino-3-pyridinyl)-1H-indol-5-amine	-67%	-87%	-41%	-85%	-27%	-81%
N-(4-Amino-3-pyridinyl)-1-methyl-1H-indol-5-amine	-42%	-62%				
N-(3-Amino-4-pyridinyl)-1H-indol-5-amine		-82%	-37%			

* difference in edema vs.control

TABLE 1 (continued)

Compound	PIPE* (0.1 M)	PLA_2* (0.01 M)	AAEE (1 mg)	TPAEE (10 μg)	in vivo DNA (25 mg)	in vitro DNA (50 μM)
3-[(1H-Indol-5-yl)-oxy]-4-pyridinamine	-62%	-34%	-50%	-42%	-37%	
4-[(1H-Indol-5-yl)-oxy]-3-pyridinamine	-52%					
N-(4-Amino-3-pyridinyl)-1 H-indol-7-amine, N^7-oxide	-45%			-38%		
N-(4-Amino-3-pyridinyl)-1H-indazol-6-amine		-57%	-35%			

* difference in edema vs.control

Examples of the compound of this invention include:

N-(4-Amino-3-pyridinyl)-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-1-methyl-1H-indol-5-amine;
N-(3-Amino-4-pyridinyl)-1H-indol-5-amine;
3-[(1H-Indol-5-yl)oxy]-4-pyridinamine;
4-[(1H-Indol-5-yl)oxy]-3-pyridinamine;
N-(4-Amino-3-pyridinyl)-1H-indazol-5-amine;
N-(4-Amino-3-pyridinyl)-1H-indol-7-amine, N^7-oxide;
N-(4-Amino-3-pyridinyl)-1H-indol-7-amine;
N-(4-amino-3-pyridinyl)-1H-indazol-6-amine;
N-(4-Nitro-3-pyridinyl)-1H-indol-5-amine, N^5-oxide;
1-Methyl-N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N^5-oxide;
N-(3-Nitro-4-pyridinyl)-1H-indol-5-amine;
N-(4-Nitro-3-pyridinyl)-1H-indol-7-amine, N^7-oxide;
N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amine, N^5-oxide;
N-(4-Nitro-3-pyridinyl)-1H-indazol-6-amine, N^6-oxide;
5-[(4-Nitro-3-pyridinyl)oxy]-1H-indole, N^5-oxide;
5-[(3-Nitro-4-pyridinyl)oxy]-1H-indole;
N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine N^5-oxide;
N-(4-Amino-3-pyridinyl)-2,3-dimethyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-7-chloro-2,3-dimethyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-2,3-dimethyl-1H-indol-5-amine-N^5-oxide;
N-(4-Amino-3-pyridinyl)-N,2,3-trimethyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-2,3-dimethyl-7-iodo-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-7-chloro-2-ethyl-3-methyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-7-chloro-3-ethyl-2-methyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-2,3-dimethyl-7-trifluoromethyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-2,3-dimethyl-7-methoxy-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-3-isopropyl-2-methyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-7-chloro-2-methyl-1H-indol-5-amine;

N-(4-Amino-3-pyridinyl)-7-chloro-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-7-methyl-1H-indol-5-amine;
N-(4-Amino-3-pyridinyl)-3-ethyl-1H-indol-5-amine; and
N-(4-Amino-3-pyridinyl)-7-bromo-2,3-dimethyl-1H-indol-5-amine.

The following examples are presented in order to illustrate this invention:

EXAMPLE 1

N-(4-Nitro-3-pyridinyl)-1H-indol-5-amine, N^5-oxide

A solution of 3-fluoro-4-nitropyridine-1-oxide[1] (5 g) and 1H-indol-5-amine (4.2 g) in 100 ml ethanol was warmed to 80° for one hour and thereafter cooled, and the product was filtered to give 8 g solid, d 244°. Three grams were recrystallized from acetonitrile to give 2.6 g solid, d 244-245°.

ANALYSIS:			
Calculated for $C_{13}H_{10}N_4O_3$	57.77%C	3.73%H	20.74%N
Found	57.99%C	3.66%H	20.91%N

EXAMPLE 2

1-Methyl-N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N^5-oxide

A solution of 3-fluoro-4-nitropyridine-1-oxide (6 g) and 1-methyl-1H-indol-5-amine (5.5 g) in 125 ml ethanol was warmed on a steam bath for thirty minutes and thereafter cooled, diluted with ether and filtered to give 10 g solid, d 232-234°. Three grams were recrystallized from ethanol to give 2.2 g needles, d 237-238°.

ANALYSIS:			
Calculated for $C_{14}H_{12}N_4O_3$	59.15%C	4.25%H	19.71%N
Found	59.31%C	4.20%H	19.71%N

EXAMPLE 3

N-(3-Nitro-4-pyridinyl)-1H-indol-5-amine

To 150 ml of absolute ethanol were added 1H-indol-5-amine (8.06 g), 4-chloro-3-nitropyridine (10.0 g) and triethylamine (8.5 ml), and this mixture was heated to 60°C and stirred for 2 hours. The mixture was cooled, the ethanol evaporated, and the residue taken up in a water/ethyl acetate mixture. This was treated with Na_2CO_3 (aq) to adjust the pH to 10. The organic layer was collected, the aqueous layer extracted again with ethyl acetate, and the organics were combined, washed with water and dried (sat. NaCl, anh. $MgSO_4$).

After filtration, the solvent was evaporated to yield a solid (14.2 g) which was eluted with 5% ethyl acetate/DCM on a silica gel column via flash method. The desired fractions were concentrated to yield a solid (6.1 g). Of this material, 2.0 g was recrystallized from absolute ethanol to yield a solid, 1.2 g, m.p. 204-206°C.

ANALYSIS:			
Calculated for $C_{13}H_{10}N_4O_2$	61.41%C	3.96%H	22.04%N
Found	61.41%C	3.96%H	22.00%N

EXAMPLE 4

N-(4-Nitro-3-pyridinyl)-1H-indol-7-amine, N^7-oxide

To 200 ml ethanol were added 3-fluoro-4-nitropyridine-1-oxide (6.0 g) and 1H-indol-7-amine (5.5 g). After stirring at 85°C for four hours, the mixture was cooled, and the precipitate was collected, washed with methanol, and dried at

[1] Talik and Talik, Rocaniki Chemii 38, 777 (1964).

60°C overnight to give 9.9 g of solid, m.p. 250°C.

ANALYSIS:			
Calculated for $C_{13}H_{10}N_4O_3$	57.78%C	3.73%H	20.73%N
Found	57.37%C	3.54%H	20.40%N

EXAMPLE 6

N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amine, N^5-oxide

A mixture of 3-fluoro-4-nitropyridine-1-oxide (6 g) and 1H-indazol-5-amine (5.2 g) in 150 ml of ethanol was refluxed for two hours, and thereafter was cooled, diluted with ether and filtered to give 10 g solid. A 3.5 g portion was recrystallized from ethanol to give 3.0 g solid, d 250°.

ANALYSIS:			
Calculated for $C_{12}H_9N_5O_3$	53.13%C	3.34%H	25.83%N
Found	52.84%C	3.34%H	25.36%N

EXAMPLE 7

N-(4-Nitro-3-pyridinyl)-1H-indazol-6-amine, N^6-oxide

To 100 ml of ethanol were added 3-fluoro-4-nitropyridine-1-oxide (6.0 g) and 1H-indazol-6-amine (5.5 g) and this mixture was heated to 70°C and stirred for four hours. The mixture was filtered to yield a solid (9.5 g) which was recrystallized from methanol to yield a solid, 6.0 g, m.p. 247-248°C (decomposed).

ANALYSIS :			
Calculated for $C_{12}H_9N_5O_3$	53.14%C	3.34%H	25.82%N
Found	52.96%C	3.17%H	25.72%N

EXAMPLE 8

5-[(4-Nitro-3-pyridinyl)oxy]-1H-indole, N^5-oxide

A solution of 5-hydroxyindole (4.8 g) in 20 ml dimethylformamide was slowly added to an ice cooled suspension of sodium hydride (0.9 g) in 5 ml dimethylformamide. After the anion formation, a solution of 3-fluoro-4-nitropyridine-1-oxide (5.7 g) in 20 ml dimethylformamide was added. After one hour the reaction mixture was stirred with ice water, extracted with chloroform and filtered. The organic extract was washed with water and saturated sodium chloride solution, dried (anhy. $MgSO_4$), filtered and concentrated to 3.5 g oil. This oil was purified by flash chromatography (silica, 20% ethyl acetate in dichloromethane) to give 2.2 g solid, d 208-210°. This was combined with 2 g product obtained from another condensation and recrystallized from ethanol to give 3 g, d 216-218°.

ANALYSIS:			
Calculated for $C_{13}H_9N_3O_4$	57.57%C	3.34%H	15.49%N
Found	57.41%C	3.36%H	15.39%N

EXAMPLE 9

5-[(3-nitro-4-pyridinyl)oxy]-1H-indole

To a solution of 5-hydroxyindole (7.45 g) in 100 ml of DMF was added K_2CO_3 (10.4 g). This mixture was stirred for 10 minutes at room temperature and then a solution of 4-chloro-3-nitropyridine (11.89 g) in 50 ml DMF was added dropwise. The reaction was allowed to proceed for 24 hours at room temperature. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl solution and dried over

$MgSO_4$. After filtration, the solvent was evaporated to yield an oil (15.4 g). This material was eluted with 5% ethyl acetate/DCM on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid, 1.35 g, m.p. 182-184°C.

EXAMPLE 10

N-(4-Amino-3-pyridinyl)-1H-indol-5-amine

A mixture of N-(4-nitro-3-pyridinyl)-1H-indol-5-amine, N^5-oxide (7.8 g) in 500 ml ethanol containing platinum oxide (1.25 g) was hydrogenated at 3.45 x 10^5 Pa (50 psi) for six hours and thereafter filtered and concentrated. The product was purified by flash chromatography (silica, 20% methanol in dichloromethane) to give 6 g solid, m.p. 83-90°. Three grams were distilled twice via Kugelrohr [240-250° @ 1.33 Pa (0.01 mm Hg] to give 2.4 g solid, 138-140°.

ANALYSIS:			
Calculated for $C_{13}H_{12}N_4$	69.62%C	5.39%H	24.99%N
Found	69.21%C	5.47%H	24.80%N

EXAMPLE 11

N-(4-Amino-3-pyridinyl)-1-methyl-1H-indol-5-amine

A suspension of 1-methyl-N-(4-nitro-3-pyddinyl)-1H-indol-5-amine, N^5-oxide (6.8 g) in 250 ml ethanol containing 0.4 g platinum oxide was hydrogenated at 3.45 x 10^5 Pa (50 psi) for twenty hours and thereafter filtered through Celite (Trade Mark) and concentrated to 3.5 g oil. This oil was purified by HPLC (silica 20% methanol in ethyl acetate) to give 2.5 g solid, m.p. 167-169°. This solid was recrystallized from acetonitrile/ether to give 1.1 g solid, m.p. 168-169°.

ANALYSIS:			
Calculated for $C_{14}H_{14}N_4$	70.57%C	5.92%H	24.51%N
Found	70.44%C	5.96%H	23.39%N

EXAMPLE 12

N-(3-Amino-4-pyridinyl)-1H-indol-5-amine

To a slurry of 10% Pd/C (1.0 g) in 10 ml of methanol was added N-(3-nitro-4-pyridinyl)-1H-indol-5-amine (4.0 g) in 230 ml methanol and this mixture was hydrogenated at 3.45 x 10^5 Pa (50 psi) on a Parr apparatus. When the reaction was complete, the mixture was filtered through Celite (Trade Mark) and the filtrate concentrated to yield a solid (3.9 g). This material was eluated with 20 % methanol/DCM on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.45 g) which was recrystallized from ethanol/water (10:1) to yield a solid, 1.8 g, m.p. 159-161°C.

ANALYSIS:			
Calculated for $C_{13}H_{12}N_4$	69.62%C	5.39%H	24.98%N
Found	69.63%C	5.46%H	25.07%N

EXAMPLE 13

3-[(1H-Indol-5-yl)oxy]-4-pyridinamine

A suspension of 5-[(4-nitro-3-pyridinyl)oxy]-1H-indole, N^5-oxide (10 g) in 250 ml ethanol containing 0.4 g PtO_2 was hydrogenated at 3.45 x 10^5 Pa (50 psi) for 25 hours and thereafter filtered through Celite (Trade Mark) and concentrated to 9 g oil. This oil was purified by HPLC (silica, 10 % methanol in ethyl acetate) to give 3.5 g solid. This solid was recrystallized from acetonitrile to give 2.4 g crystals, m.p. 170-172°.

ANALYSIS:			
Calculated for $C_{13}H_{11}N_3O$	69.32%C	4.92%H	18.65%N
Found	69.28%C	4.80%H	18.57%N

EXAMPLE 15

4-[(1H-Indol-5-yl)oxy]-3-pyridinamine

To a slurry of 10% Pd/C (1.0 g) in 10 ml of ethanol was added 5-[(3-nitro-4-pyridinyl)oxy]-1H-indole (3.7 g) in 240 ml ethanol and this was shaken on a Parr apparatus for 1 hour. The mixture was filtered and the filtrate concentrated to yield an oil (3.1 g) which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to an oil which solidified on standing to yield 2.6 g, m.p. 155-157°C.

ANALYSIS:			
Calculated for $C_{13}H_{11}N_3O$	69.32%C	4.92%H	18.65%N
Found	69.13%C	4.94%H	18.46%N

EXAMPLE 16

N-(4-Amino-3-pyridinyl)-1H-indazol-5-amine

A suspension of N-(4-nitro-3-pyddinyl)-1H-indazol-5-amine, N^5-oxide (7 g) in 250 ml ethanol containing 0.5 g platinum oxide was hydrogenated at 4.14 x 10^5 Pa (60 psi) for sixty hours and thereafter filtered through Celite (Trade Mark) and concentrated to 3.3 g solid. This solid was purified by HPLC (silica, 25% methanol in dichloromethane) to give 2.1 g solid. This solid was recrystallized twice from acetonitrile to give 1.5 g crystals, m.p. 198-199°

ANALYSIS:			
Calculated for $C_{12}H_{11}N_5$	63.98%C	4.92%H	31.10%N
Found	63.66%C	4.88%H	30.94%N

EXAMPLE 17

N-(4-Amino-3-pyridinyl)-1H-indol-7-amine, N^7-oxide

To 250 ml ethanol in a 500 ml Parr hydrogenation bottle were added N-(4-nitro-3-pyridinyl)-1H-indol-7-amine, N^7-oxide (5.0 g) and 0.4 g PtO_2. After shaking at ambient temperature for twenty-two hours under 3.45 x 10^5 Pa (fifty psi) hydrogen, the mixture was filtered and concentrated to a foam, 4.8 g.

This foam was eluted on a silica gel column with 30% methanol/DCM via HPLC. The desired fractions were combined and concentrated to a solid, 2.8 g, m.p. >250°C.

ANALYSIS:			
Calculated for $C_{13}H_{12}N_4O$	64.99%C	5.03%H	23.32%N
Found	64.57%C	5.12%H	22.78%N

EXAMPLE 18

N-(4-Amino-3-pyridinyl)-1H-indol-7-amine

To 250 ml ethanol in a 500 ml Parr hydrogenation bottle, were added N-(4-amino-3-pyridinyl)-1H-indol-7-amine, N^7-oxide (2.8 g) and 0.3 g PtO_2. The mixture was shaken at ambient temperature under 3.45 x 10^5 Pa (50 psi) hydrogen for one hour, and thereafter filtered and concentrated to an oil, (2.7 g). This oil was eluted on a silica gel column with 30% methanol/DCM via HPLC. The desired fractions were combined and concentrated to a solid, 2.1 g, m.p. 68-70°C.

ANALYSIS:			
Calculated for $C_{13}H_{12}N_4$	69.62%C	5.40%H	24.98%N
Found	68.98%C	5.48%H	24.79%N

EXAMPLE 19

N-(4-Amino-3-pyridinyl)-1H-indazol-6-amine

To PtO_2 (0.3 g) in 10 ml of ethanol was added N-(4-nitro-3-pyridinyl)-1H-indazol-6-amine, N^6-oxide (2.0 g) in 240 ml of ethanol and this was hydrogenated on a Parr apparatus at 4.14 x 10^5 Pa (60 psi) for 20 hours. The mixture was filtered and concentrated to an oil (2.1 g). This material was eluted with 20% methanol/DCM on a silica gel column via HPLC. The desired fractions were concentrated to a solid (0.7 g), which was recrystallized from acetonitrile to yield a solid 0.5 g, m.p. 214-216°C.

ANALYSIS:			
Calculated for $C_{12}H_{11}N_5$	63.99%C	4.92%H	31.09%N
Found	64.16%C	4.92%H	31.23%N

EXAMPLE 20

N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine ethanolate

A mixture of 4-nitro-3-fluoropyridine N-oxide (5.4 g) and 5-amino-2-methylindole (5.0 g) in 100 mL of thoroughly degassed absolute ethanol was stirred at 50°C for 30 minutes and then cooled slowly to 0°C. The precipitate was collected and air dried to give 9.0 g of N-(4-nitro-3-pyridinyl)-2-methyl-1H-indol-5-amine N^5-oxide as a powder. This powder was taken up in 135 mL of isopropanol and hydrogenated at 50°C over 3% platinum on carbon at 3.45 x 10^5 Pa (50 psi) in the presence of lithium hydroxide (0.26 g). Filtration and concentration left 8.0 g of a solid which was recrystallized from 32 mL of methanol giving 4.9 g of crystals. This material was then azeotroped repeatedly with absolutc ethanol and dried at 85°C to give 2.4 g of crystals, mp = 96-98°C.

ANALYSIS:			
Calculated for $C_{16}H_{20}N_4O$	67.58%C	7.09%H	19.70%N
Found	67.50%C	7.05%H	19.88%N

EXAMPLE 21

N-(4-Amino-3-pyridinyl)-2-methyl-1H-indol-5-amine N^5-oxide hemihydrate

A mixture of 4-nitro-3-fluoropyridine N-oxide (5.4 g) and 5-amino-2-methylindole (5.0 g) in 100 mL of thoroughly degassed absolute ethanol was stirred at 50°C for 30 minutes and then cooled slowly to 0°C. The precipitate was collected and air dried to give 8.2 g of N-(4-nitro-3-pyridinyl)-2-methyl-1H-indol-5-amine N^5-oxide as a powder. This powder was taken up in 255 mL of absolute ethanol and hydrogenated at room temperature over 3% platinum on carbon at 3.45 x 10^5 Pa (50 psi). Filtration and concentration left 6.4 of a solid which was purified by HPLC (7:3 dichloromethane/methanol) to give 3.0 g of a powder which was recrystallized from methanol/ether to give 1.8 g of crystals, m.p. 178-180 (with gas evolution).

ANALYSIS:			
Calculated for $C_{14}H_{14}N_4O \cdot 0.5H_2O$	63.86%C	5.74%H	21.24%N
Found	63.70%C	5.85%H	20.84%N

EXAMPLE 22

N-(4-Amino-3-pyridinyl)-2,3-dimethyl-1H-indol-5-amine ethanolate

A mixture of 4-nitro-3-fluoropyridine N-oxide (4.2 g) and 5-amino-2,3-dimethylindole (4.2 g) in 100 mL of thoroughly degassed absolute ethanol was stirred at 50°C for 30 minutes and then cooled slowly to 0°C. The precipitate was collected and air dried to give 7.3 g of N-(4-nitro-3-pyridinyl)-2,3-dimethyl-1H-indol-5-amine N^5-oxide as a powder. This powder was taken up in 225 mL of isopropanol and hydrogenated at 50°C over 3% platinum on carbon at 3.45 x 10^5 Pa (50 psi) in the presence of lithium hydroxide (0.21 g). Filtration and concentration left 4.7 g of a solid which was recrystallized twice from methanol giving 3.4 g of crystals. This material was then azeotroped repeatedly with absolute ethanol and dried at 85° to give 1.4 g of crystals, mp = 112-115°C.

ANALYSIS:			
Calculated for $C_{17}H_{22}N_4O$	68.43%C	7.43%H	18.78%N
Found	68.31%C	7.50%H	18.61%N

EXAMPLE 23

N-(4-Amino-3-pyridinyl)-7-chloro-2,3-dimethyl-1H-indol-5-amine

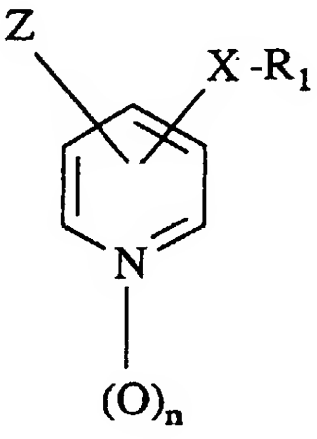
A mixture of 4-nitro-3-fluoropyridine N-oxide (1.2 g) and 5-amino-7-chloro-2,3-dimethylindole (1.4 g) in thoroughly degassed absolute ethanol was stirred at 50°C for 30 minutes and thereafter cooled slowly to 0°C. The precipitate was collected and air-dried to give 2.37 g of N-(4-nitro-3-pyridinyl)-7-chloro-2,3-dimethyl-1H-indol-5-amine N^5-oxide as a powder.

This powder was added in portions to a slurry of titanium powder, prepared from 2.28 g of titanium tetrachloride and 0.45 g of lithium aluminum hydride, in tetrahydrofuran at 0°C. The reaction mixture was warmed to room temperature and stirred for four hours. The reaction mixture was quenched with dilute ammonium hydroxide and extracted into chloroform. Evaporation of the solvent left a solid which was purfied by flash chromatography to give 1.2 g of a powder, m.p. 108-110°C.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE.

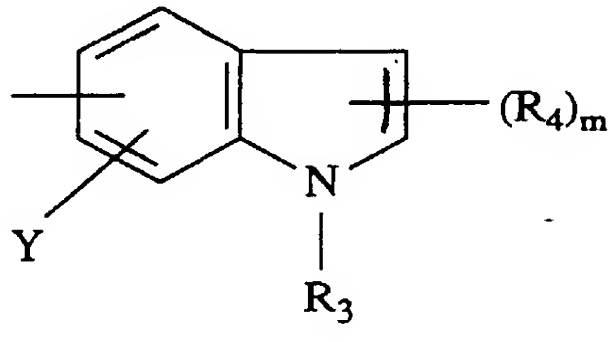
1. A compound having the formula I,



where

n is 0 or 1;
X is O or NR_2, R_2 being hydrogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkylcarhonyl;
Z is NO_2 or NHR
where

R is hydrogen, (C_1-C_6)-alkyl, phenyl-(C_1-C_6)-alkyl where the phenyl is optionally mono-substituted with a (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, halogen or trifluoromethyl group, or (C_1-C_6)-alkylcarbonyl; and
R_1 is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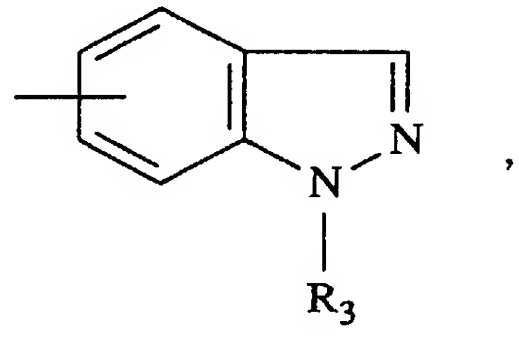
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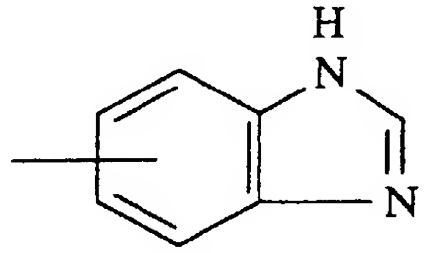
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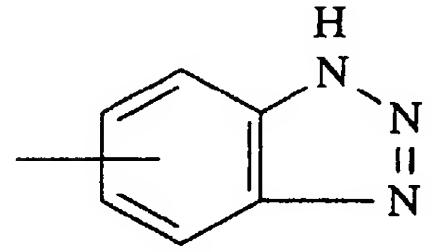
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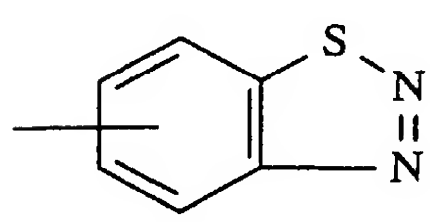
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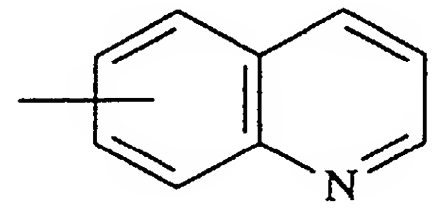
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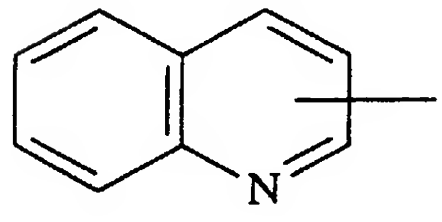
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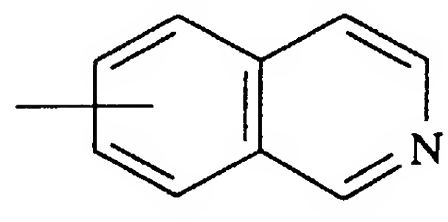
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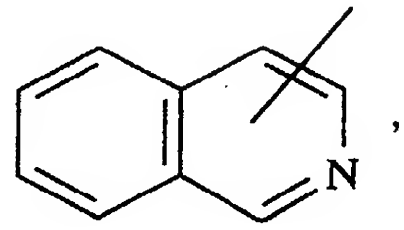
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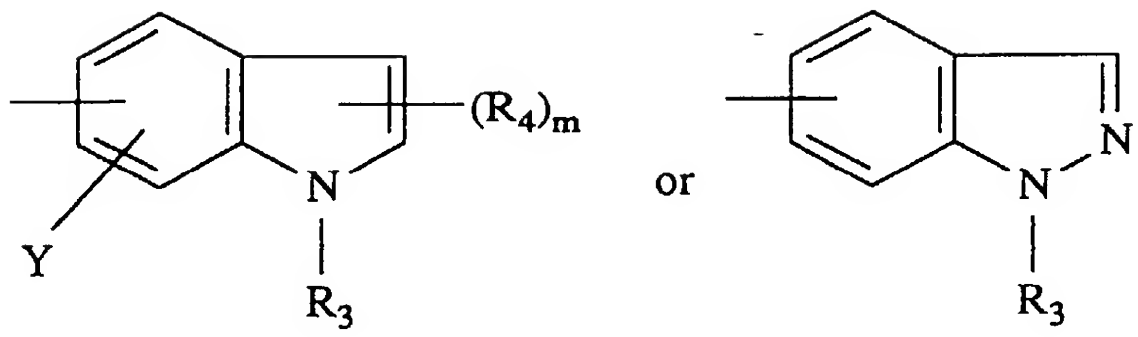
wherein R_3 is hydrogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkylcarbonyl; m is 1 or 2; each R_4 is independently hydrogen or (C_1-C_6)-alkyl; and Y is hydrogen, halogen, (C_1-C_6-alkyl, (C_1-C_6)-alkoxy or trifluoromethyl;
but excluding the compound 4-{5-nitro-2-pyridyloxy}-indol;

or a pharmaceutically acceptable acid salt thereof.

2. A compound as defined in claim 1, where X is O or NH, and Z is NO_2 or NH_2.

3. A compound as defined in claim 2, where R_1 is



where Y is hydrogen or halogen, and R_3, R_4 and m are as defined in claim 1.

4. A compound as defined in claim 3, where Y is hydrogen or chlorine, R_3 is hydrogen, methyl or acetyl and R_4 is hydrogen or methyl.

5. A compound as defined in claim 4, where n is O and Z is NH_2.

6. The compound as defined in claim 5, which is
N-(4-amino-3-pyridinyl)-1H-indol-5-amine or a pharmaceutically acceptable acid addition salt thereof.

7. The compound as defined in claim 5, which is
3-[(1H-indol-5-yl)oxy]-4-pyridin-amine or a pharmaceutically acceptable acid addition salt thereof.

8. A compound as defined in claim 4 where n is 1 and Z is NO_2.

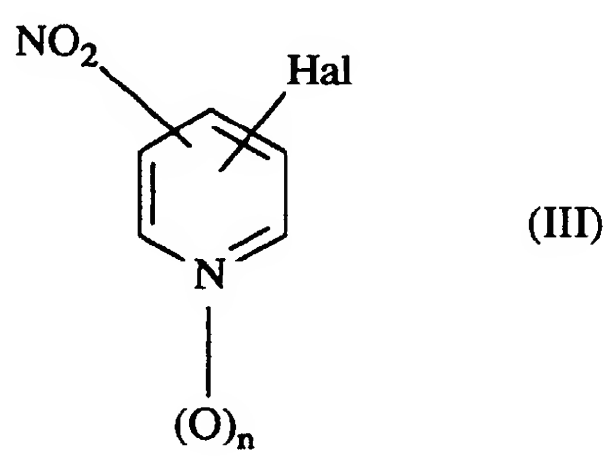
9. The compound as defined in claim 8, which is N-(4-nitro-3-pyridinyl)-1H-indazol-5-amine, N^5-oxide.

10. A pharmaceutical composition which comprises as the active ingredient a compound as defined in claim 1 and a suitable carrier therefor.

11. Use of a compound as defined in claim 1 for the preparation of a medicament being effective against skin disorders.

12. A process for the preparation of a compound as defined in claim 1, which comprises

a) reacting a compound of the formula III



(III)

where Hal is F or Cl and n is as defined in claim 1 with a compound of the formula R_1-OH or R_1-OM, where R_1 is as defined in claim 1 and M is Li, Na or K, to afford a compound of the formula I, where R_1 and n are as defined, X is 0 and Z is NO_2, or

b) reacting a compound of the formula III with R_1-NH_2 where R_1 is as defined in claim 1, to afford a compound of the formula I where R_1 and n are as defined, X is NH and Z is NO_2,

c) optionally reacting a compound of the formula I, where R_1 and n are as defined in claim 1, X is NH and Z is NO_2, with a compound of the formula R_2-Hal where Hal is Cl or Br and R_2 is (C_1-C_6)-alkyl or (C_1-C_6)-alkylcarbonyl, to afford a compound of the formula I, where R_1 and n are as defined, X is NR_2, R_2 being as defined and Z is NO_2,

d) optionally selectively hydrogenating a compound of the formula I, where R_1 and X are as defined in claim 1, n is 1 and Z is NO_2, to afford a compound of the formula I, where R_1 and X are as defined, n is 1 and Z is NH_2, or

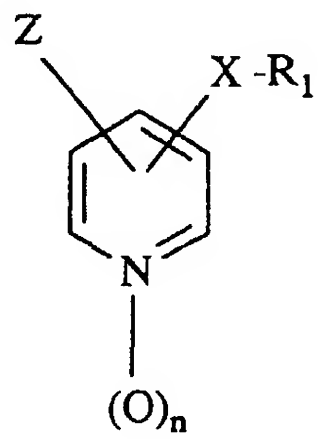
e) optionally catalytically hydrogenating a compound of the formula I, where R_1 and X are as defined in claim 1, n is 1 and Z is NO_2, to afford a compound of the formula I, where X and R_1 are as defined, n is 0 and Z is NH_2,

f) optionally reacting a compound of the formula I, where X, R_1 and n are as defined in claim 1, and Z is NH_2, with a compound of the formula R_5-Hal, where R_5 is $(C_1$-$C_6)$-alkyl, phenyl-$(C_1$-$C_6)$-alkyl where the phenyl is optionally mono-substituted with a $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, halogen or trifluoromethyl group, or $(C_1$-$C_6)$-alkylcarbonyl and Hal is Br or Cl, to afford a compound of the formula I, where X, R_1 and n are as defined and Z is NHR_5 where R_5 is as defined

g) optionally reducing a compound of the formula I, where R_1 and X are as defined in claim 1, n is 1 and Z is NO_2, with a titanium (0) reagent to afford a compound of the formula I where R_1 and X are as defined, n is 0 and Z is NH_2.

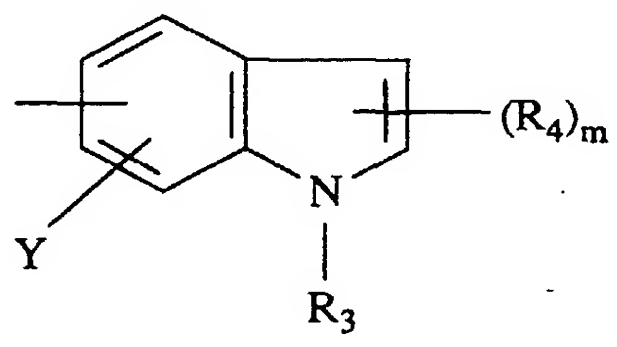
Claims for the following Contracting States : ES, GR

1. A process for the preparation of a compound of the formula I,



where

n is 0 or 1;
X is O or NR_2, R_2 being hydrogen, $(C_1$-$C_6)$-alkyl or $(C_1$-$C_6)$-alkylcarbonyl;
Z is NO_2 or NHR
where
R is hydrogen, $(C_1$-$C_6)$-alkyl, phenyl-$(C_1$-$C_6)$-alkyl where the phenyl is optionally mono-substituted with a $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, halogen or trifluoromethyl group, or $(C_1$-$C_6)$-alkylcarbonyl; and
R_1 is



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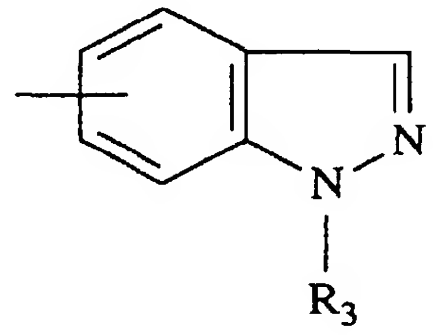

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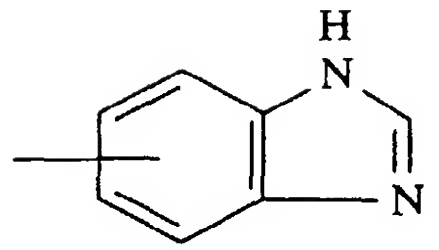
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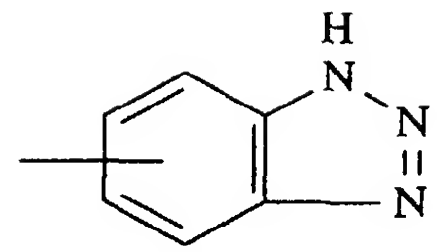
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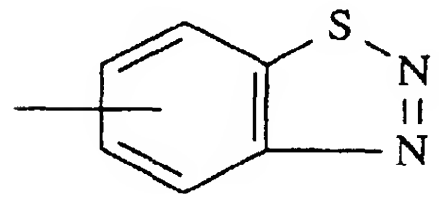
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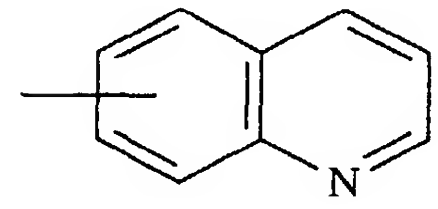
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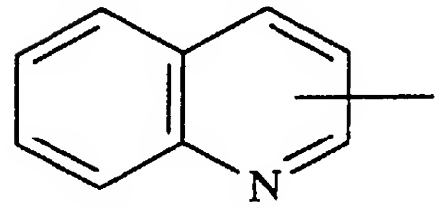
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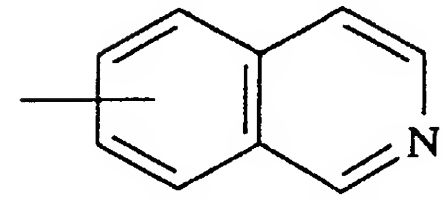
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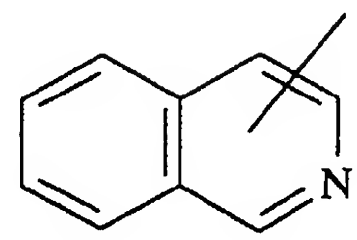
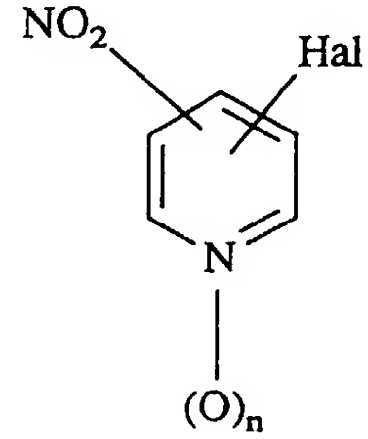
or


,

wherein R_3 is hydrogen, $(C_1\text{-}C_6)$-alkyl or $(C_1\text{-}C_6)$-alkylcarbonyl; m is 1 or 2; each R_4 is independently hydrogen or $(C_1\text{-}C_6)$-alkyl; and Y is hydrogen, halogen, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkoxy or trifluoromethyl;
but excluding the compound 4-(5-nitro-pyridyloxy)-indol;

or a pharmaceutically acceptable acid salt thereof which comprises

a) reacting a compound of the formula III


(III)

where Hal is F or Cl and n is as defined-above with a compound of the formula R_1-OH or R_1-OM, where R_1 is as defined above and M is Li, Na or K, to afford a compound of the formula I, where R_1 and n are as defined, X is 0 and Z is NO_2, or

b) reacting a compound of the formula III with R_1-NH_2 where R_1 is as defined above, to afford a compound of the formula I where R_1 and n are as defined, X is NH and Z is NO_2,

c) optionally reacting a compound of the formula I, where R_1 and n are as defined above, X is NH and Z is NO_2, with a compound of the formula R_2-Hal where Hal is Cl or Br and R_2 is $(C_1$-$C_6)$-alkyl or $(C_1$-$C_6)$-alkylcarbonyl, to afford a compound of the formula I, where R_1 and n are as defined, X is NR_2, R_2 being as defined and Z is NO_2,

d) optionally selectively hydrogenating a compound of the formula I, where R_1 and X are as defined above, n is 1 and Z is NO_2, to afford a compound of the formula I, where R_1 and X are as defined, n is 1 and Z is NH_2, or

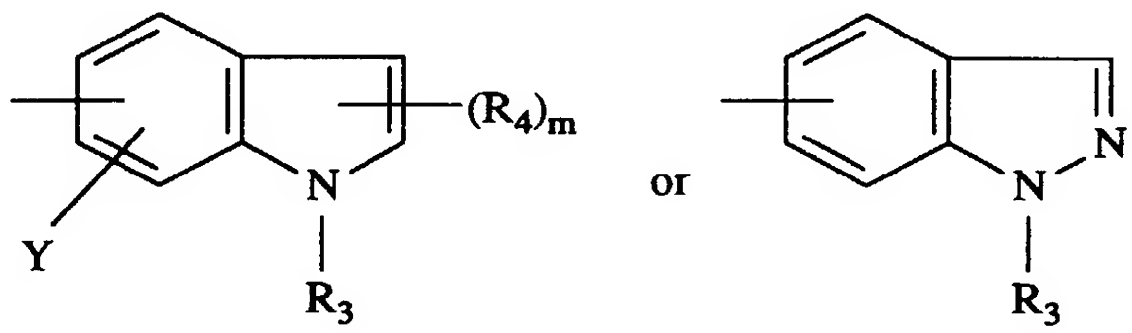
e) optionally catalytically hydrogenating a compound of the formula I, where R_1 and X are as defined above, n is 1 and Z is NO_2, to afford a compound of the formula I, where X and R_1 are as defined, n is 0 and Z is NH_2,

f) optionally reacting a compound of the formula I, where X, R_1 and n are as defined above, and Z is NH_2, with a compound of the formula R_5-Hal, where R_5 is $(C_1$-$C_6)$-alkyl, phenyl-$(C_1$-$C_6)$-alkyl where the phenyl is optionally mono-substituted with a $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, halogen or trifluoromethyl group, or $(C_1$-$C_6)$-alkylcarbonyl and Hal is Br or Cl, to afford a compound of the formula I, where X, R_1 and n are as defined and Z is NHR_5 where R_5 is as defined,

g) optionally reducing a compound of the formula I, where R_1 and X are as defined above, n is 1 and Z is NO_2, with a titanium (0) reagent to afford a compound of the formula I where R_1 and X are as defined, n is 0 and Z is NH_2.

2. A process as defined in claim 1, wherein X is 0 or NH, and Z is NO_2 or NH_2.

3. A process as defined in claim 2, where R_1 is



where Y is hydrogen or halogen, and R_3, R_4 and m are as defined in claim 1.

4. A process as defined in claim 3, where Y is hydrogen or chlorine, R_3 is hydrogen, methyl or acetyl and R_4 is hydrogen or methyl.

5. A process as defined in claim 4, where n is 0 and Z is NH_2.

6. The process as defined in claim 5, wherein
N-(4-amino-3-pyridinyl)-1H-indol-5-amine or a pharmaceutically acceptable acid addition salt thereof is prepared.

7. The process as defined in claim 5, wherein
3-[(1H-indol-5-yl)oxy]-4-pyridin-amine or a pharmaceutically acceptable acid addition salt thereof is prepared.

8. A process as defined in claim 4 where n is 1 and Z is NO_2.

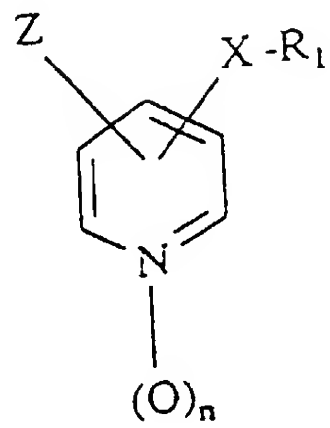
9. The process as defined in claim 8, wherein
N-(4-nitro-3-pyridinyl)-1H-indazol-5-amine, N^5-oxide is prepared.

10. Use of a compound as defined in claim 1 for the preparation of a medicament being effective against skin disorders.

Patentansprüche

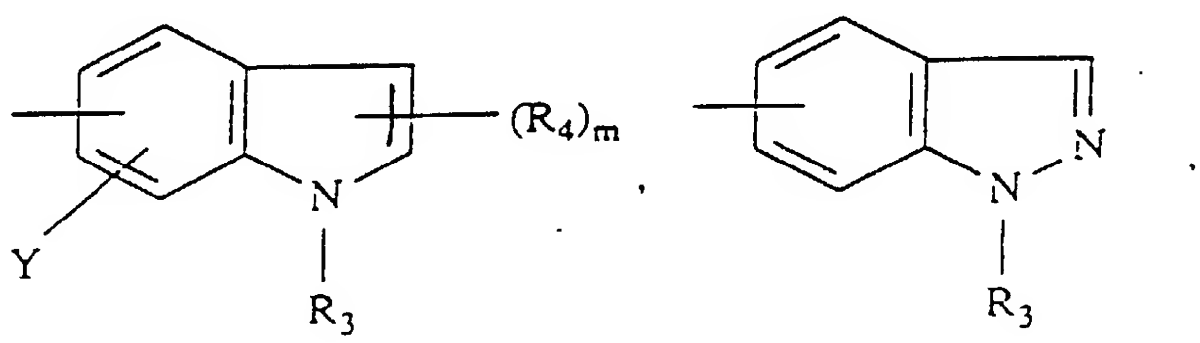
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

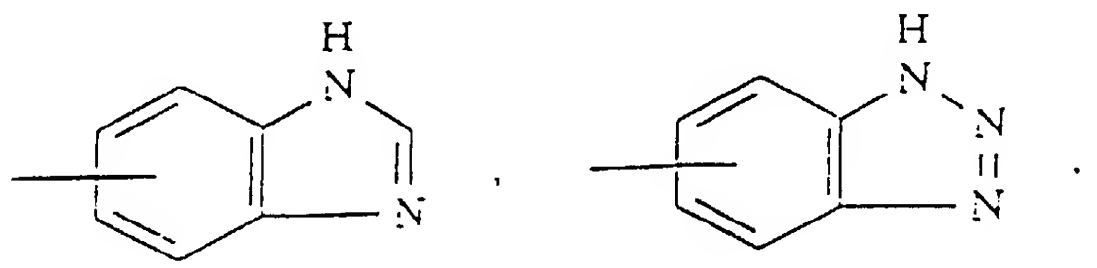
1. Verbindung der Formel I

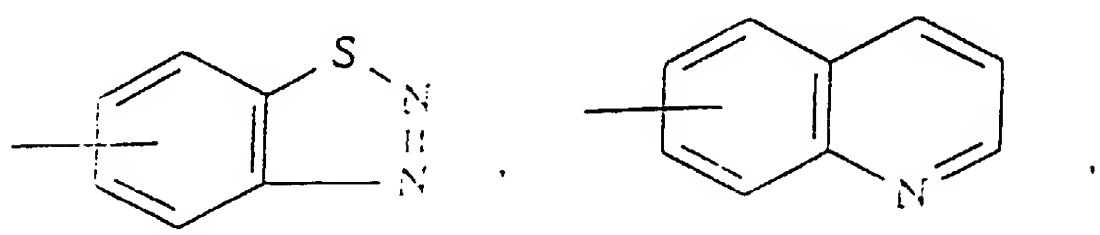


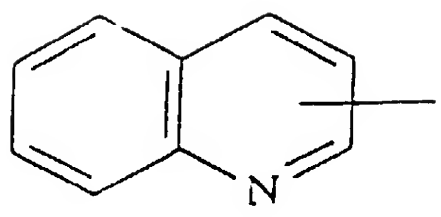
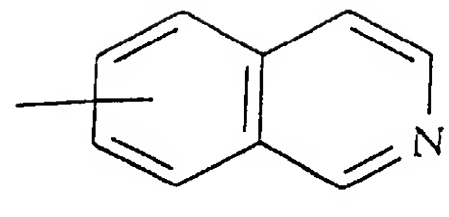
in welcher

n gleich 0 oder 1 ist;
X für O oder NR_2 steht, wobei R_2 Wasserstoff, $(C_1\text{-}C_6)$-Alkyl oder $(C_1\text{-}C_6)$-Alkylcarbonyl bezeichnet;
Z für NO_2 oder NHR steht,
wobei
R für Wasserstoff, $(C_1\text{-}C_6)$-Alkyl, Phenyl-$(C_1\text{-}C_6)$-alkyl, wobei Phenyl wahlweise durch eine $(C_1\text{-}C_6)$-Alkyl-, $(C_1\text{-}C_6)$-Alkoxy-, Halogen- oder Trifluormethylgruppe monosubstituiert ist, oder $(C_1\text{-}C_6)$-Alkylcarbonyl steht; und
R_1 für

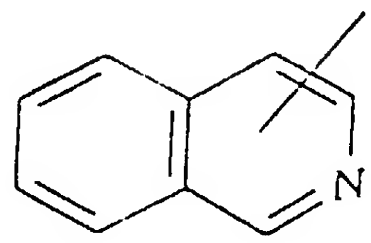






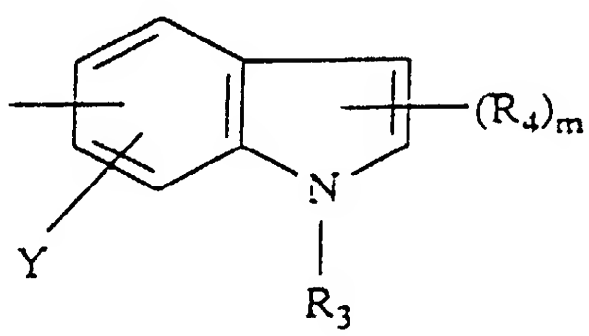
oder



steht, wobei R_3 für Wasserstoff, (C_1-C_6)-Alkyl oder (C_1-C_6)-Alkylcarbonyl steht; m gleich 1 oder ist; jedes R_4 unabhängig voneinander fiir Wasserstoff oder (C_1-C_6)-Alkyl steht; und Y für Wasserstoff, Halogen, (C_1-C_6)-Alkyl, (C_1-C_6)-Alkoxy oder Trifluormethyl steht;
jedoch ausgenommen die Verbindung 4-(5-Nitro-2-pyridyloxy)-indol;
oder ein pharmazeutisch verträgliches Säuresalz davon.

2. Verbindung gemäß Anspruch 1, wobei X für O oder NH steht und Z NO_2 oder NH_2 bezeichnet.

3. Verbindung gemäß Anspruch 2, wobei R_1 für



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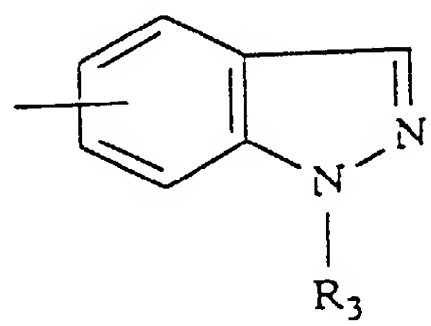


steht, dabei bezeichnet Y Wasserstoff oder Halogen, und R_3, R_4 und m kommt die in Anspruch 1 angewiesene Bedeutung zu.

4. Verbindung gemäß Anspruch 3, wobei Y für Wasserstoff oder Chlor steht, R_3 Wasserstoff, Methyl oder Acetyl bezeichnet und R_4 Wasserstoff oder Methyl ist.

5. Verbindung gemäß Anspruch 4, wobei n gleich 0 ist und Z für NH_2 steht.

6. Verbindung gemäß Anspruch 5, die N-(4-Amino-3-pyridinyl)-1H-indol-5-amin oder ein pharmazeutisch verträgliches Säureadditionssalz davon ist.

7. Verbindung gemäß Anspruch 5, die 3-[(1H-indol-5-yl)oxy]-4-pyridinamin oder ein pharmazeutisch verträgliches Säureadditionssalz davon ist.

8. Verbindung gemäß Anspruch 4, wobei n gleich 1 ist und Z für NO_2 steht.

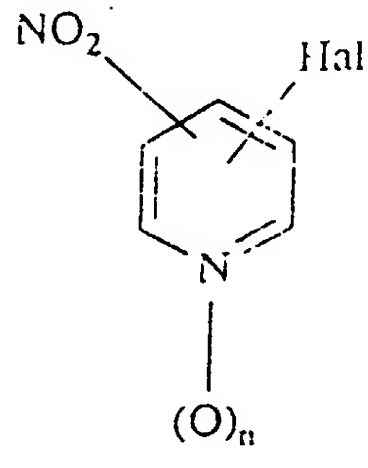
9. Verbindung gemäß Anspruch 8, die N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amin, N^5-Oxid ist.

10. Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß Anspruch 1 als Wirkstoff und eine geeignete Trägersubstanz dafür.

11. Verwendung einer Verbindung gemäß Anspruch 1 zur Herstellung eines Arzneimittels, das gegen Hauterkrankungen wirksam ist.

12. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, umfassend

a) die Umsetzung einer Verbindung der Formel III



(III)

in welcher Hal für F oder Cl steht und n die in Anspruch 1 angewiesene Bedeutung zukommt, mit einer Verbindung der Formel R_1-OH oder R_1-OM, wobei R_1 die in Anspruch 1 angewiesene Bedeutung zukommt und M für Li, Na oder K steht, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und n die angewiesene Bedeutung zukommt, X gleich 0 ist und Z für NO_2 steht, oder

b) die Umsetzung einer Verbindung der Formel III mit R_1-NH_2, in der R_1 die in Anspruch 1 angewiesene Bedeutung zukommt, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und n die angewiesene Bedeutung zukommt, X für NH und Z für NO_2 steht,

c) wahlweise die Umsetzung einer Verbindung der Formel I, in der R_1 und n die in Anspruch 1 angewiesene Bedeutung zukommt, X für NH steht und Z NO_2 ist, mit einer Verbindung der Formel R_2-Hal, in der Hal für Cl oder Br steht und R_2 (C_1-C_6)-Alkyl oder (C_1-C_6)-Alkylcarbonyl bezeichnet, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und n die angewiesene Bedeutung zukommt, X für NR_2 steht, wobei R_2 die genannte Bedeutung hat, und Z für NO_2 steht,

d) wahlweise die selektive Hydrierung einer Verbindung der Formel I, in welcher R_1 und X die in Anspruch 1 angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NO_2 steht, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und X die angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NH_2 steht, oder

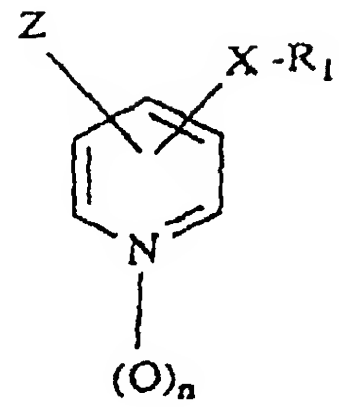
e) wahlweise die katalytische Hydrierung einer Verbindung der Formel I, in welcher R_1 und X die in Anspruch 1 angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NO_2 steht, zur Herstellung einer Verbindung der Formel I, in welcher X und R_1 die angewiesene Bedeutung zukommt, n gleich 0 ist und Z für NH_2 steht,

f) wahlweise die Umsetzung einer Verbindung der Formel I, in der X, R_1 und n die in Anspruch 1 angewiesene Bedeutung zukommt und Z für NH_2 steht, mit einer Verbindung der Formel R_5-Hal, in der R_5 für (C_1-C_6)-Alkyl, Phenyl-(C_1-C_6)-alkyl, wobei Phenyl wahlweise durch eine (C_1-C_6)-Alkyl-, (C_1-C_6)-Alkoxy-, Halogen- oder Trifluormethylgruppe monosubstituiert ist, oder (C_1-C_6)-Alkylcarbonyl steht und Hal Br oder Cl bezeichnet, zur Herstellung einer Verbindung der Formel I, in welcher X, R_1 und n die angewiesene Bedeutung zukommt und Z für NHR_5 steht, wobei R_5 die genannte Bedeutung hat,

g) wahlweise die Reduktion einer Verbindung der Formel I, in der R_1 und X die in Anspruch 1 angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NO_2 steht, mit einem Titan(0)-Reagenz zur Herstellung einer Verbindung der Formel I, in welcher R_1 und X die angewiesene Bedeutung zukommt, n gleich 0 ist und Z für NH_2 steht.

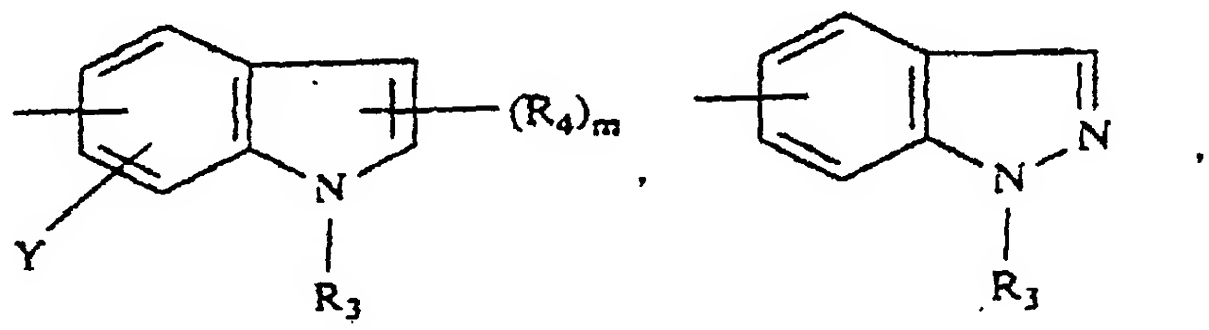
Patentansprüche für folgende Vertragsstaaten : ES, GR

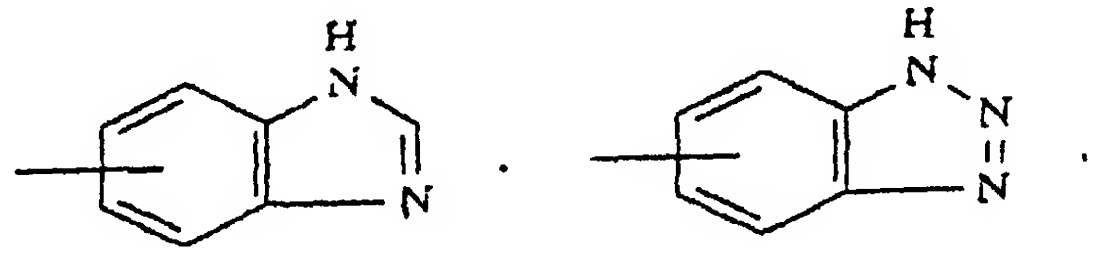
1. Verfahren zur Herstellung einer Verbindung der Formel I

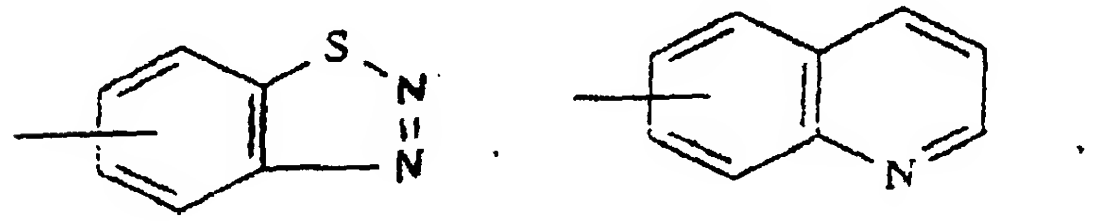


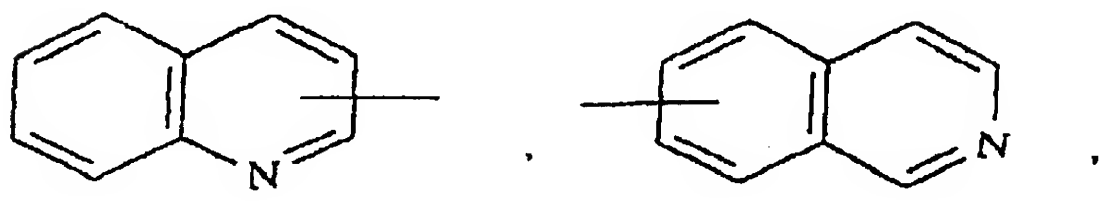
in welcher

n gleich 0 oder ist;
X für O oder NR_2 steht, R_2 Wasserstoff, $(C_1$-$C_6)$-Alkyl oder $(C_1$-$C_6)$-Alkylcarbonyl bezeichnet;
Z für NO_2 oder NHR steht,
wobei
R für Wasserstoff, $(C_1$-$C_6)$-Alkyl, Phenyl-$(C_1$-$C_6)$-alkyl, wobei Phenyl wahlweise durch eine $(C_1$-$C_6)$-Alkyl-, $(C_1$-$C_6)$-Alkoxy-, Halogen- oder Trifluormethylgruppe monosubstituiert ist, oder $(C_1$-$C_6)$-Alkylcarbonyl steht; und
R_1 für









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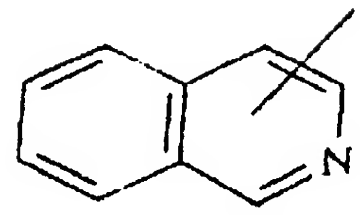
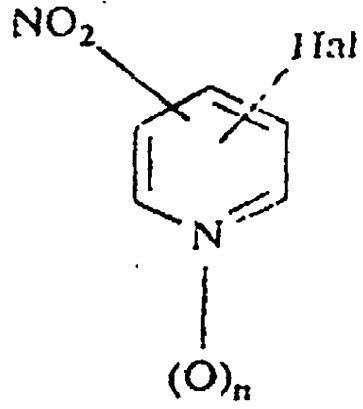


steht, wobei R_3 für Wasserstoff, $(C_1\text{-}C_6)$-Alkyl oder $(C_1\text{-}C_6)$-Alkylcarbonyl steht; m gleich 1 oder 2 ist; jedes R_4 unabhängig voneinander für Wasserstoff oder $(C_1\text{-}C_6)$-Alkyl steht; und Y für Wasserstoff, Halogen, $(C_1\text{-}C_6)$-Alkyl, $(C_1\text{-}C_6)$-Alkoxy oder Trifluormethyl steht;
jedoch ausgenommen die Verbindung 4-(5-Nitro-2-pyridyloxy)-indol;
oder ein pharmazeutisch verträgliches Säuresalz davon, umfassend

a) die Umsetzung einer Verbindung der Formel III



(III)

in welcher Hal für F oder Cl steht und n die in Anspruch 1 angewiesene Bedeutung zukommt, mit einer Verbindung der Formel R_1-OH oder R_1-OM, wobei R_1 die in Anspruch 1 angewiesene Bedeutung zukommt und M für Li, Na oder K steht, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und n die angewiesene Bedeutung zukommt, X gleich 0 ist und Z für NO_2 steht, oder

b) die Umsetzung einer Verbindung der Formel III mit R_1-NH_2, in der R_1 die in Anspruch 1 angewiesene Bedeutung zukommt, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und n die angewiesene Bedeutung zukommt, X für NH und Z für NO_2 steht,

c) wahlweise die Umsetzung einer Verbindung der Formel I, in der R_1 und n die vorstehend angewiesene Bedeutung zukommt, X für NH steht und Z NO_2 ist, mit einer Verbindung der Formel R_2-Hal, in der Hal für Cl oder Br steht und R_2 $(C_1\text{-}C_6)$-Alkyl oder $(C_1\text{-}C_6)$-Alkylcarbonyl bezeichnet, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und n die angewiesene Bedeutung zukommt, X für NR_2 steht, wobei R_2 die genannte Bedeutung hat, und Z für NO_2 steht,

d) wahlweise die selektive Hydrierung einer Verbindung der Formel I, in welcher R_1 und X die vorstehend angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NO_2 steht, zur Herstellung einer Verbindung der Formel I, in welcher R_1 und X die angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NH_2 steht, oder

e) wahlweise die katalytische Hydrierung einer Verbindung der Formel I, in welcher R_1 und X die vorstehend angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NO_2 steht, zur Herstellung einer Verbindung der Formel I, in welcher X und R_1 die angewiesene Bedeutung zukommt, n gleich 0 ist und Z für NH_2 steht,

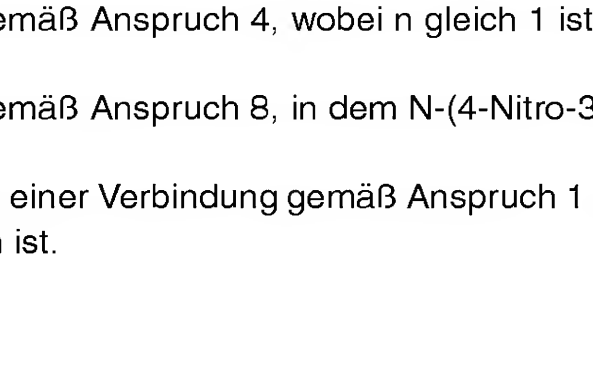
f) wahlweise die Umsetzung einer Verbindung der Formel I, in der X, R_1 und n die vorstehend angewiesene Bedeutung zukommt und Z für NH_2 steht, mit einer Verbindung der Formel R_5-Hal, in der R_5 für $(C_1\text{-}C_6)$-Alkyl, Phenyl-$(C_1\text{-}C_6)$-alkyl, wobei Phenyl wahlweise durch eine $(C_1\text{-}C_6)$-Alkyl-, $(C_1\text{-}C_6)$-Alkoxy-, Halogen- oder Trifluormethylgruppe monosubstituiert ist, oder $(C_1\text{-}C_6)$-Alkylcarbonyl steht und Hal Br oder Cl bezeichnet, zur Herstellung einer Verbindung der Formel I, in welcher X, R_1 und n die angewiesene Bedeutung zukommt und Z für NHR_5 steht, wobei R_5 die genannte Bedeutung hat,

g) wahlweise die Reduktion einer Verbindung der Formel I, in der R_1 und X die vorstehend angewiesene Bedeutung zukommt, n gleich 1 ist und Z für NO_2 steht, mit einem Titan(0)-Reagenz zur Herstellung einer

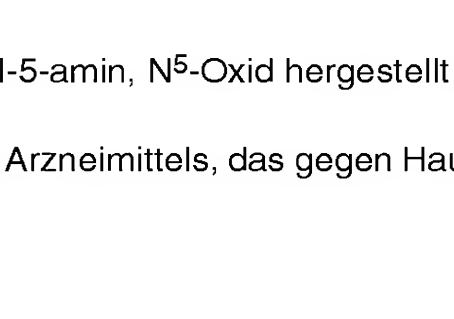
Verbindung der Formel I, in welcher R_1 und X die angewiesene Bedeutung zukommt, n gleich 0 ist und Z für NH_2 steht.

2. Verfahren gemäß Anspruch 1, wobei X für O oder NH steht und Z NO_2 oder NH_2 bezeichnet.

3. Verfahren gemäß Anspruch 2, wobei R_1 für



oder



steht, dabei bezeichnet Y Wasserstoff oder Halogen, und R_3, R_4 und m kommt die in Anspruch 1 angewiesene Bedeutung zu.

4. Verfahren gemäß Anspruch 3, wobei Y für Wasserstoff oder Chlor steht, R_3 Wasserstoff, Methyl oder Acetyl bezeichnet und R_4 Wasserstoff oder Methyl ist.

5. Verfahren gemäß Anspruch 4, wobei n gleich 0 ist und Z für NH_2 steht.

6. Verfahren gemäß Anspruch 5, in dem N-(4-Amino-3-pyridinyl)-1H-indol-5-amin oder ein pharmazeutisch verträgliches Säureadditionssalz davon hergestellt wird.

7. Verfahren gemäß Anspruch 5, in dem 3-[(1H-indol-5-yl)oxy]-4-pyridinamin oder ein pharmazeutisch verträgliches Säureadditionssalz davon hergestellt wird.

8. Verfahren gemäß Anspruch 4, wobei n gleich 1 ist und Z für NO_2 steht.

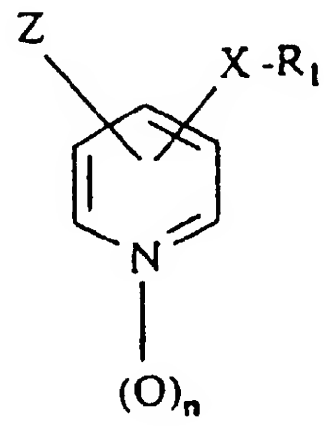
9. Verfahren gemäß Anspruch 8, in dem N-(4-Nitro-3-pyridinyl)-1H-indazol-5-amin, N^5-Oxid hergestellt wird.

10. Verwendung einer Verbindung gemäß Anspruch 1 zur Herstellung eines Arzneimittels, das gegen Hauterkrankungen wirksam ist.

Revendications

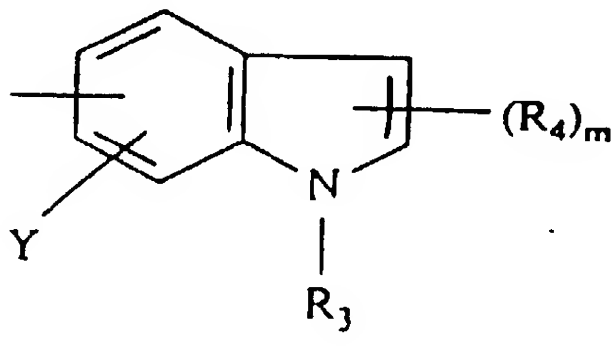
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule I



dans laquelle

n est 0 ou 1;
X représente O ou NR_2, R_2 étant un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ou alkyl(C_1-C_6)-carbonyle;
Z représente NO_2 ou NHR,
R étant un atome d'hydrogène ou un groupe alkyle en C_1-C_6, phényl-alkyle(C_1-C_6) dans lequel le fragment phényle est éventuellement monosubstitué par un atome d'halogène ou par un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6 ou trifluorométhyle, ou alkyl(C_1-C_6)-carbonyle, et
R_1 est



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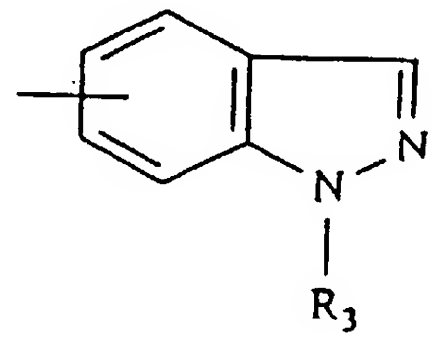

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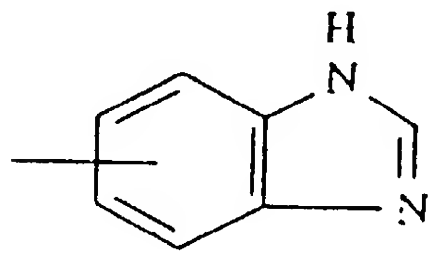

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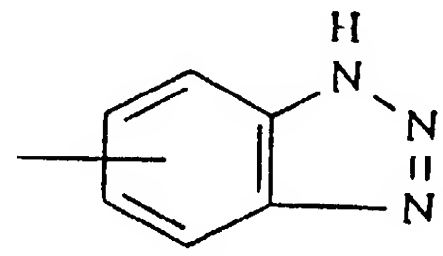

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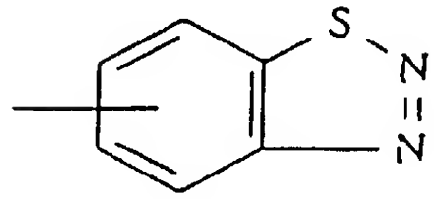

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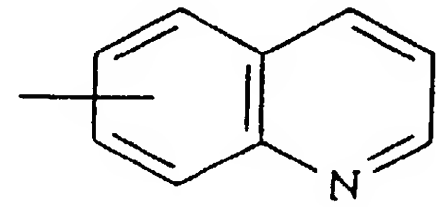

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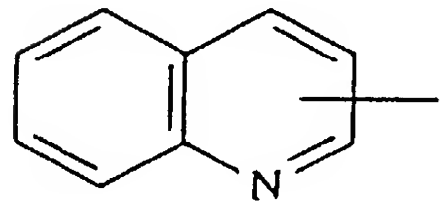

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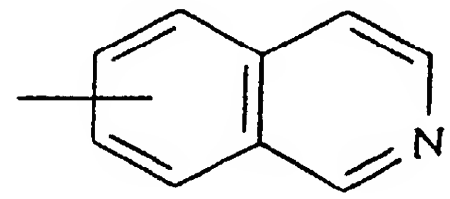

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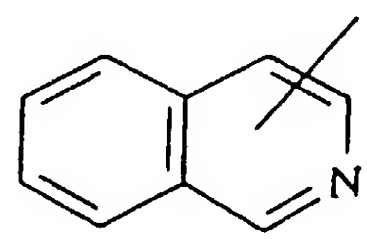


,

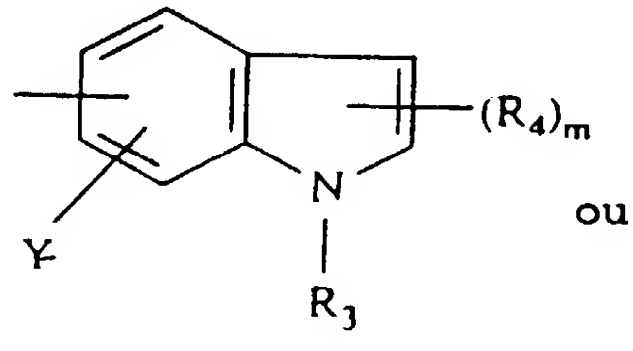
R_3 étant
un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ou alkyl(C_1-C_6)-carbonyle; m étant 1 ou 2; chaque radical R_4 représentant indépendamment un atome d'hydrogène ou un groupe alkyle en C_1-C_6; et Y représentant

un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6 ou trifluorométhyle;

mais à l'exclusion du composé 4-(5-nitro-2-pyridyloxy)-indole;
ou sel d'addition avec un acide pharmaceutiquement acceptable d'un tel composé.

2. Composé selon la revendication 1, dans lequel X représente O ou NH, et Z représente NO_2 ou NH_2.

3. Composé selon la revendication 2, dans lequel R_1 est



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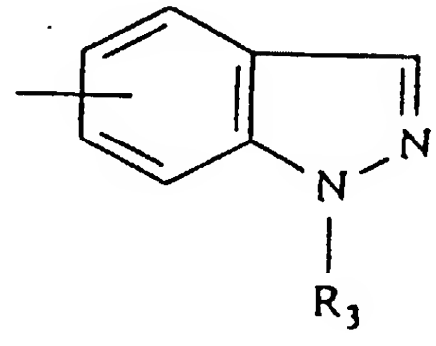


Y étant un atome d'hydrogène ou d'halogène, et R_3, R_4 et m étant tels que définis dans la revendication 1.

4. Composé selon la revendication 3, dans lequel Y est un atome d'hydrogène ou de chlore, R_3 est un atome d'hydrogène ou le groupe méthyle ou acétyle, et R_4 est un atome d'hydrogène ou le groupe méthyle.

5. Composé selon la revendication 4, dans lequel n est égal à 0 et Z est NH_2.

6. Composé selon la revendication 5, qui est la N-(4-amino-3-pyridinyl)-1H-indole-5-amine ou un sel d'addition avec un acide pharmaceutiquement acceptable de celle-ci.

7. Composé selon la revendication 5, qui est la 3-[(1H-indole-5-yl)oxy]-4-pyridine-amine ou un sel d'addition avec un acide pharmaceutiquement acceptable de celle-ci.

8. Composé selon la revendication 4, dans lequel n est égal à 1 et Z est NO_2.

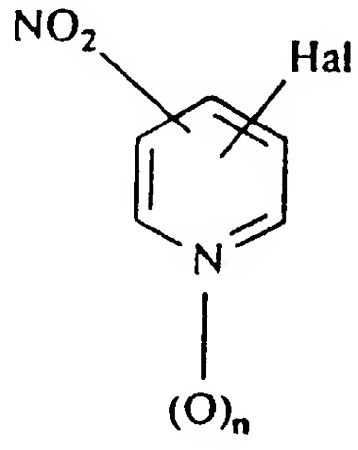
9. Composé selon la revendication 8, qui est le N^5-oxyde de N-(4-nitro-3-pyridinyl)-1H-indazole-5-amine.

10. Composition pharmaceutique, comprenant en tant que composant actif un composé tel que défini dans la revendication 1, et un véhicule approprié pour celui-ci.

11. Utilisation d'un composé tel que défini dans la revendication 1, pour la fabrication d'un médicament efficace contre les affections de la peau.

12. Procédé pour la préparation d'un composé selon la revendication 1, comprenant

a) la mise en réaction d'un composé de formule III

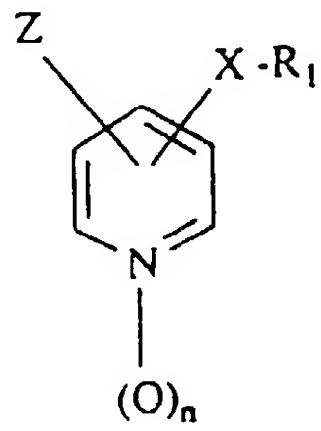


(III)

dans laquelle Hal est F ou Cl et n est tel que défini dans la revendication 1, avec un composé de formule R_1-OH ou R_1-OM, dans laquelle R_1 est tel que défini dans la revendication 1 et M est Li, Na ou K, pour l'obtention d'un composé de formule I dans lequel R_1 et n sont tels que définis, X représente O et Z représente NO_2, ou
b) la mise en réaction d'un composé de formule III avec R_1-NH_2, R_1 étant tel que défini dans la revendication 1, pour l'obtention d'un composé de formule I dans lequel R_1 et n sont tels que définis, X représente NH et Z est NO_2,
c) éventuellement la mise en réaction d'un composé de formule I dans lequel R_1 et n sont tels que définis dans la revendication 1, X représente NH et Z est NO_2, avec un composé de formule R_2-Hal, dans laquelle Hal est Cl ou Br et R_2 est un groupe alkyle en C_1-C_6 ou alkyl(C_1-C_6)-carbonyle, pour l'obtention d'un composé de formule I dans lequel R_1 et n sont tels que définis, X est NR_2, R_2 étant tel que défini et Z est NO_2,
d) éventuellement l'hydrogénation sélective d'un composé de formule I dans lequel R_1 et X sont tels que définis dans la revendication 1, n est égal à 1 et Z représente NO_2, pour l'obtention d'un composé de formule I dans lequel R_1 et X sont tels que définis, n est égal à 1 et Z est NH_2, ou
e) éventuellement l'hydrogénation catalytique d'un composé de formule I dans lequel R_1 et X sont tels que définis dans la revendication 1, n est égal à 1 et Z représente NO_2, pour l'obtention d'un composé de formule I dans lequel X et R_1 sont tels que définis, n est égal à 0 et Z est NH_2,
f) éventuellement la mise en réaction d'un composé de formule I dans lequel X, R_1 et n sont tels que définis dans la revendication 1, et Z est NH_2, avec un composé de formule R_5-Hal, dans laquelle R_5 est un groupe alkyle en C_1-C_6 ou phényl-alkyle(C_1-C_6) dans lequel le fragment phényle est éventuellement monosubstitué par un atome d'halogène ou par un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6 ou trifluorométhyle, ou alkyl(C_1-C_6)-carbonyle, et Hal est Br ou Cl, pour l'obtention d'un composé de formule I dans lequel X, R_1 et n sont tels que définis et Z est NHR_5, R_5 étant tel que défini,
g) éventuellement la réduction d'un composé de formule I, dans lequel R_1 et X sont tels que définis dans la revendication 1, n est égal à 1 et Z représente NO_2, avec un réactif à base de titane-(0), pour l'obtention d'un composé de formule I dans lequel R_1 et X sont tels que définis, n est égal à 0 et Z est NH_2.

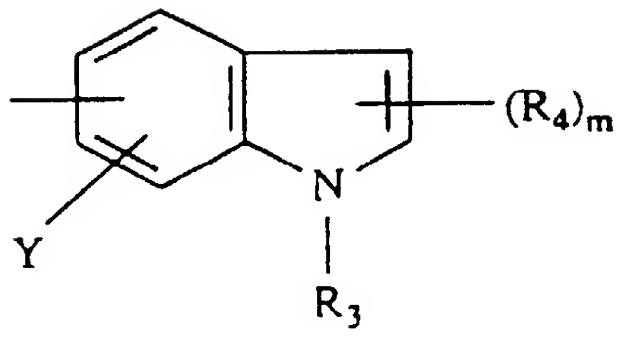
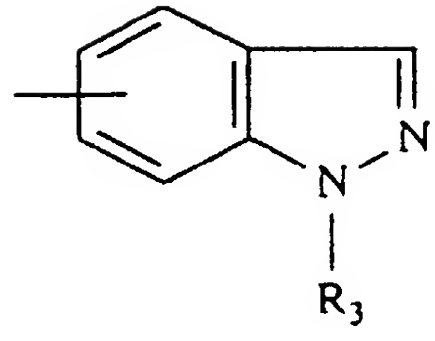
Revendications pour les Etats contractants suivants : ES, GR

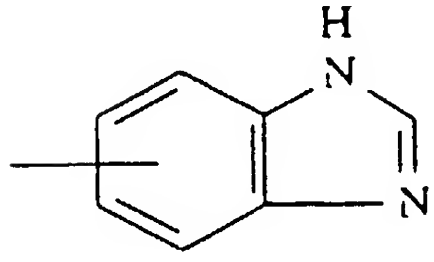
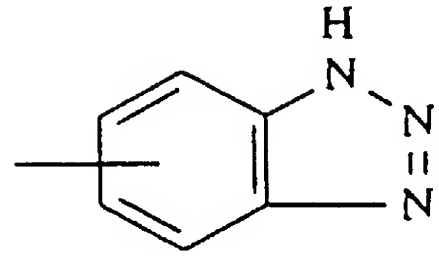
1. Procédé pour la préparation d'un composé de formule I

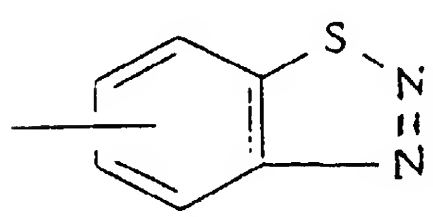
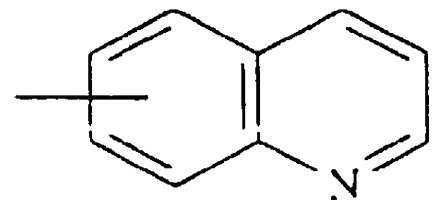


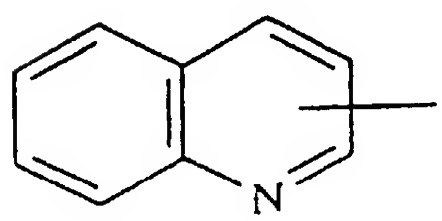
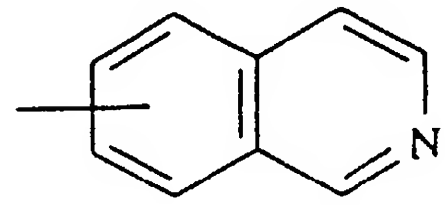
dans laquelle

n est 0 ou 1;
X représente O ou NR_2, R_2 étant un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ou alkyl(C_1-C_6)-carbonyle;
Z représente NO_2 ou NHR,
R étant un atome d'hydrogène ou un groupe alkyle en C_1-C_6, phényl-alkyle(C_1-C_6) dans lequel le fragment phényle est éventuellement monosubstitué par un atome d'halogène ou par un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6 ou trifluorométhyle, ou alkyl(C_1-C_6)-carbonyle, et
R_1 est

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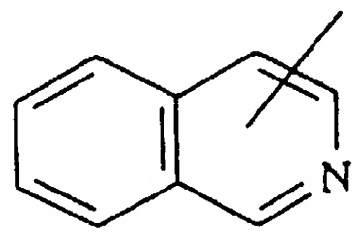
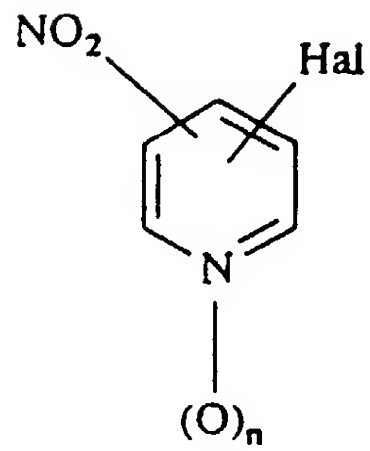


R_3 étant un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ou alkyl(C_1-C_6)-carbonyle; m étant 1 ou 2; chaque radical R_4 représentant indépendamment un atome d'hydrogène ou un groupe alkyle en C_1-C_6; et Y représentant un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6 ou trifluorométhyle;

mais à l'exclusion du composé 4-(5-nitro-2-pyridyloxy)-indole;
ou d'un sel d'addition avec un acide pharmaceutiquement acceptable d'un tel composé, comprenant

a) la mise en réaction d'un composé de formule III



(III)

dans laquelle Hal est F ou Cl et n est tel que défini plus haut, avec un composé de formule R_1-OH ou R_1-OM, dans laquelle R_1 est tel que défini plus haut et M est Li, Na ou K, pour l'obtention d'un composé de formule I dans lequel R_1 et n sont tels que définis, X représente O et Z représente NO_2, ou

b) la mise en réaction d'un composé de formule III avec R_1-NH_2, R_1 étant tel que défini plus haut, pour l'obtention d'un composé de formule I dans lequel R_1 et n sont tels que définis, X représente NH et Z est NO_2,

c) éventuellement la mise en réaction d'un composé de formule I dans lequel R_1 et n sont tels que définis plus haut, X représente NH et Z est NO_2, avec un composé de formule R_2-Hal, dans laquelle Hal est Cl ou Br et R_2 est un groupe alkyle en C_1-C_6 ou alkyl(C_1-C_6)-carbonyle, pour l'obtention d'un composé de formule I dans lequel R_1 et n sont tels que définis, X est NR_2, R_2 étant tel que défini et Z est NO_2,

d) éventuellement l'hydrogénation sélective d'un composé de formule I dans lequel R_1 et X sont tels que définis plus haut, n est égal à 1 et Z représente NO_2, pour l'obtention d'un composé de formule I dans lequel R_1 et X sont tels que définis, n est égal à 1 et Z est NH_2, ou

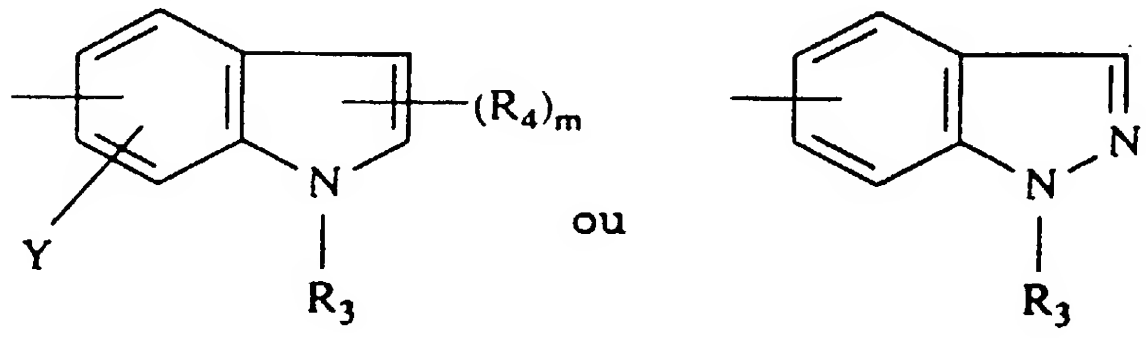
e) éventuellement l'hydrogénation catalytique d'un composé de formule I dans lequel R_1 et X sont tels que définis plus haut, n est égal à 1 et Z représente NO_2, pour l'obtention d'un composé de formule I dans lequel X et R_1 sont tels que définis, n est égal à 0 et Z est NH_2,

f) éventuellement la mise en réaction d'un composé de formule I dans lequel X, R_1 et n sont tels que définis plus haut, et Z est NH_2, avec un composé de formule R_5-Hal, dans laquelle R_5 est un groupe alkyle en C_1-C_6 ou phényl-alkyle(C_1-C_6) dans lequel le fragment phényle est éventuellement monosubstitué par un atome d'halogène ou par un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6 ou trifluorométhyle, ou alkyl(C_1-C_6)-carbonyle, et Hal est Br ou Cl, pour l'obtention d'un composé de formule I dans lequel X, R_1 et n sont tels que définis et Z est NHR_5, R_5 étant tel que défini,

g) éventuellement la réduction d'un composé de formule I, dans lequel R_1 et X sont tels que définis plus haut, n est égal à 1 et Z représente NO_2, avec un réactif à base de titane-(0), pour l'obtention d'un composé de formule I dans lequel R_1 et X sont tels que définis, n est égal à 0 et Z est NH_2.

2. Procédé selon la revendication 1, dans lequel X représente O ou NH, et Z représente NO_2 ou NH_2.

3. Procédé selon la revendication 2, dans lequel R_1 est



Y étant un atome d'hydrogène ou d'halogène, et R_3, R_4 et m étant tels que définis dans la revendication 1.

4. Procédé selon la revendication 3, dans lequel Y est un atome d'hydrogène ou de chlore, R_3 est un atome d'hydrogène ou le groupe méthyle ou acétyle, et R_4 est un atome d'hydrogène ou le groupe méthyle.

5. Procédé selon la revendication 4, dans lequel n est égal à 0 et Z est NH_2.

6. Procédé selon la revendication 5, dans lequel on prépare la N-(4-amino-3-pyridinyl)-1H-indole-5-amine ou un sel d'addition avec un acide pharmaceutiquement acceptable de celle-ci.

7. Procédé selon la revendication 5, dans lequel on prépare la 3-[(1H-indole-5-yl)oxy]-4-pyridine-amine ou un sel d'addition avec un acide pharmaceutiquement acceptable de celle-ci.

8. Procédé selon la revendication 4, dans lequel n est égal à 1 et Z est NO_2.

9. Procédé selon la revendication 8, dans lequel on prépare le N^5-oxyde de N-(4-nitro-3-pyridinyl)-1H-indazole-5-amine.

10. Utilisation d'un composé tel que défini dans la revendication 1, pour la fabrication d'un médicament efficace contre les affections de la peau.